Exhibit E

UNITED STATES DISTRICT COURT
SOUTHERN DISTRICT OF WEST VIRGINIA
AT CHARLESTON

IN RE: ETHICON, INC., PELVIC REPAIR SYSTEM PRODUCTS LIABILITY LITIGATION **THIS DOCUMENT RELATES TO WAVE 1**	**Master File No. 2:12-MD-02327** **JOSEPH R. GOODWIN** **U.S. DISTRICT JUDGE**

RULE 26 EXPERT REPORT OF ANNE M. WEBER

I have reviewed the documents and materials identified in this report and the Appendices, including the reliance list set forth at Appendix A. Based upon the analysis of these documents and materials, as well as my knowledge, experience, and training, set forth in my Curriculume Vitae attached as Appendix B, I have formed opinions with regard to the Ethicon/Gynecare Prolift Pelvic Floor Repair Systems. Each of the opinions set forth herein is held to a reasonable degree of medical certainty.

Glossary of Terms

Gynecare:
A brand name used by Ethicon to identify products marketed to treat female pelvic health conditions.

Prolene Mesh:
A nonabsorbable polypropylene mesh marketed by Ethicon for use in hernia surgery; also used off-label for prolapse surgery.

Prolene Soft Mesh:
A nonabsorbable polypropylene mesh marketed by Ethicon for use in hernia surgery; also used off-label for prolapse surgery. Prolene Soft mesh is a lighter density formulation of Prolene mesh.

GYNECARE GYNEMESH® PS Nonabsorbable PROLENE® Soft Mesh:
A nonabsorbable polypropylene mesh marketed by Ethicon for use in prolapse surgery, of the same construction as Prolene Soft mesh marketed by Ethicon for use in hernia surgery. Gynemesh PS

mesh is sold in standard rectangular shapes measuring 10×15cm and 25×25cm. In this report, it is referred to as Gynemesh PS mesh.

GYNECARE PROLIFT® Pelvic Floor Repair Systems:
"Kits" containing pre-shaped Gynemesh PS mesh and inserter tools, marketed by Ethicon for use in vaginal prolapse surgery, implanted using what Ethicon termed the "revolutionary" Prolift procedure, which is the TVM procedure. There are three separate kits: Prolift Total, Anterior, and Posterior Pelvic Floor Repair Systems. The Total Pelvic Floor Repair System is used to treat apical, anterior, and posterior vaginal prolapse. The Anterior Pelvic Floor Repair System is used to treat anterior vaginal prolapse. The Posterior Pelvic Floor Repair System is used to treat apical posterior vaginal prolapse. In this report, they are referred to in general as Prolift, Prolift Pelvic Floor Repair Systems, Prolift Systems, or specifically as the type of Prolift System (total, anterior, or posterior).

ULTRAPRO™ Synthetic Partially Absorbable Mesh:
A mesh constructed of a combination of absorbable and nonabsorbable components, poliglecaprone and polypropylene, respectively, marketed by Ethicon for use in hernia surgery. In this report, it is referred to as Ultrapro mesh.

GYNECARE Gynemesh M mesh:
A mesh constructed of a combination of absorbable and nonabsorbable components, poliglecaprone and polypropylene, respectively, of the same construction as Ultrapro mesh marketed by Ethicon for use in hernia surgery. Gynemesh M mesh is only sold by Ethicon as a component of the Prolift + M Systems (see below). In this report, it is referred to as Gynemesh M mesh.

GYNECARE Prolift + M™ Pelvic Floor Repair Systems:
"Kits" containing pre-shaped Gynemesh M mesh and inserter tools, marketed by Ethicon for use in vaginal prolapse surgery, implanted using what Ethicon termed the "revolutionary" Prolift procedure, which is the TVM procedure. Identical to the Prolift kits in all but the mesh material, there are three separate Prolift + M kits: Prolift + M Total, Anterior, and Posterior Pelvic Floor Repair Systems. In this report, they are referred to as Prolift + M, Prolift + M Pelvic Floor Repair Systems, Prolift + M Systems, or specifically as the type of Prolift + M System (total, anterior, or posterior).

Pelvic Organ Prolapse
Pelvic organ prolapse (POP) is a clinical condition in which the pelvic organs have lost their normal support and are displaced to a lower-than-normal position. Normally, vaginal support provides support to the adjacent organs, the uterus, bladder, and rectum. (Important in maintaining urinary continence, the urethra relies in part on the vagina for support and also has some independent support of its own.) The vagina is normally supported by a network of connective tissue, termed the endopelvic fascia, that holds the upper two-thirds of the vagina over a muscular plate, the levator ani raphe.[1] When muscular function is impaired, the connective tissue supports

[1] Delancey JO. Anatomic aspects of vaginal eversion after hysterectomy. Am J Obstet Gynecol 1992; 166 (6 Pt 1): 1717-1728.

cannot sustain the unnatural stresses, and they stretch or break over time.[2] Without normal vaginal support, the adjacent organs "drop" or "fall" from their normal positions in the pelvis.

Anterior vaginal prolapse refers to loss of support affecting the anterior vagina and thus the bladder. Previously termed "cystocele," anterior vaginal prolapse is the preferred term to emphasize vaginal support loss as the primary etiology, reflecting no structural abnormality of the bladder itself, just lost support. Functional abnormalities of bladder emptying can occur with advanced anterior vaginal prolapse, such as incomplete bladder emptying when the anterior vagina and bladder prolapse beneath the urethra, effectively creating a "kink" in the urethra that impairs normal bladder emptying.[3] Some women with advanced prolapse find they can achieve bladder emptying by replacing the anterior vagina in the pelvis, at least temporarily restoring more normal relations between the bladder and urethra and allowing more complete bladder emptying. Stress incontinence (loss of urine with physical stress, such as coughing, laughing, or jumping) occurs commonly in association with prolapse, but it is a distinct condition of its own, not a symptom of prolapse per se.

Uterine prolapse refers to loss of support of upper vagina, which then allows the uterus to "drop" into the vaginal canal; an analogous situation, termed apical vaginal prolapse, occurs if hysterectomy had been performed previously. As with the other adjacent pelvic organs affected by vaginal support loss, it is important to recognize that the uterus is a passive "passenger" when prolapse occurs; therefore, hysterectomy alone is not a form of treatment for uterine prolapse. Enterocele is a condition in which small bowel is present behind (internal to) apical vaginal prolapse; less commonly, enterocele can also occur in conjunction with uterine prolapse. In recognition that loss of upper vaginal support is the primary etiologic event, surgical treatment of enterocele must focus on restoring that lost support; closure of the peritoneal sac that contains the small bowel is not sufficient treatment for uterine or apical vaginal prolapse.

Posterior vaginal prolapse refers to loss of support affecting the posterior vagina and thus the rectum. Previously termed "rectocele," posterior vaginal prolapse is the preferred term to emphasize vaginal support loss as the primary etiology, reflecting no structural abnormality of the rectum itself, just lost support. Functional abnormalities of rectal emptying can occur with advanced posterior vaginal prolapse, such as incomplete rectal emptying if the rectum forms a pouch behind (internal to) the posterior vagina, where stool can be trapped. Some women with advanced prolapse find they can achieve rectal emptying by replacing the posterior vagina in the pelvis, at least temporarily reducing the rectal pouch and allowing more complete rectal emptying. Fecal (or anal) incontinence (loss of stool) sometimes occurs in association with prolapse, but it is a distinct condition of its own, not a symptom of prolapse per se.

It should be acknowledged that the foregoing descriptions of prolapse affecting the different areas or compartments of the vagina are an artificial distinction to facilitate description, rather than an important pathophysiologic distinction. Prolapse most often occurs affecting more than one vaginal

[2] Norton PA. Pelvic floor disorders: the role of fascia and ligaments. Clin Obstet Gynecol 1993; 36: 926-938.
[3] Bump RC et al. The mechanism of urinary continence in women with severe uterovaginal prolapse: results of barrier studies. Obstet Gynecol 1988; 72 (3 Pt 1): 291-295.

site or compartment. Although aspects of pelvic organ support have been investigated for decades,[4] it is only relatively recently that the importance of apical vaginal support loss to the appearance of anterior vaginal prolapse has been recognized.[5] In the past, the combination of anterior and posterior vaginal prolapse were commonly treated surgically with anterior and posterior colporrhaphy, without providing specific support to the vaginal apex. It is likely that this inadequate treatment has contributed, at least in part, to the perception by some that"traditional" vaginal prolapse surgery is not as effective as desired, when in reality, the treatment was inadequate to restore all aspects of lost support.

TVM procedure:
The transvaginal mesh procedure (TVM) is a surgical procedure for the treatment of pelvic organ prolapse, using synthetic mesh that is placed vaginally. The procedure was developed by Ethicon in conjunction with a group of French physicians led by Bernard Jacquetin, beginning in about 2000.

510(k)
The FDA regulatory scheme applicable to certain medical devices, through which a medical device can be cleared by the FDA to be legally marketed in the United States if the manufacturer establishes that the medical device is "substantially equivalent" to a product that has previously been approved or cleared by the FDA.

[4] Berglas B, Rubin IC. Study of the supportive structures of the uterus by levator myography. Surg Gynecol Obstet 1953; 97: 677-692.
[5] Summers A et al. The relationship between anterior and apical compartment support. Am J Obstet Gynecol 2006; 194: 1438-1443. Epub 2006 Mar 30.
Rooney K et al. Advanced anterior vaginal wall prolapse is highly correlated with apical prolapse. Am J Obstet Gynecol 2006; 195: 1837-1840.
Lowder JL et al. The role of apical vaginal support in the appearance of anterior and posterior vaginal prolapse. Obstet Gynecol 2008; 111: 152-157.

OVERVIEW

The Prolift is an integrated system including a pre-cut, pre-shaped polypropylene mesh medical device and surgical instruments marketed for the treatment of pelvic organ prolapse pursuant to the "Prolift procedure," which is a refinement of the TVM procedure developed by Ethicon and the so-called French TVM group, a group of French gynecologists. The Prolift was first marketed as of March 2005 and was promoted as a "revolutionary" procedure for the treatment of pelvic organ prolapse. As set forth in detail herein, the Prolift is a poorly designed, inadequately studied system, implanted using a complex procedure that introduces unreasonable risks to the treatment of POP. Contrary to Ethicon's representations of safety and efficacy through the "standardized" implantation of polypropylene mesh, the Prolift offers no appreciable efficacy advantages, and presents numerous medically unsafe, and life-altering risks and complications, as compared to the alternatives such as suture-based colporrhaphy, suture fixation, and abdominal sacrocolpopexy. The Prolift implicates the devastating risk that complications due to the presence of the mesh will require multiple damaging operations that fail to resolve the patient's pain and other complications, leaving women with permanent, untreatable damage.

In marketing the Prolift Systems, Ethicon was marketing both a product and a procedure. Therefore, as multiple Ethicon witnesses have admitted in their depositions, Ethicon was responsible for ensuring the safety and effectiveness of the Prolift Systems, including the medical device consisting of precut mesh implants and specialized inserter tools, and the Prolift procedure. Ethicon failed to do so for numerous reasons, for example: (1) by failing to conduct rigorous, long-term clinical studies of the Prolift before marketing the Prolift; (2) by failing to properly evaluate clinical study data, and failing to accurately report the results; (3) by failing to ensure that medical affairs evaluated the hazards and harms that they knew would result from the Prolift, as part of the design control analysis of the Prolift, according to Ethicon's own standards, including the DDSA, FMEA,'s, and Clinical Expert Report; (4) by failing to recognize and/or acknowledge that the Prolift was not demonstrated to be safe and effective, and did not have an acceptable risk benefit profile, and marketing the Prolift to be permanently implanted in women who were unaware that they were no more than test subjects.

Ethicon violated its own credo, which is supposed to place the health and safety of the patient first, above all else.[6] Paul Parisi confirmed that the credo is "not just a sign on the wall," and that the credo provides that "the patient comes first."[7]Ethicon also violated the fundamental tenet of medicine, to "First Do No Harm," described in a 2005 PowerPoint presentation by European Scientific Director, Axel Arnaud, M.D., titled "Graft or No Graft."[8] Contrary to these principles, Ethicon marketed the Prolift, a system that causes serious complications and harm, and for which the risk/benefit profile was unacceptable.

[6] Matthew Henderson dep., 42:10-15; 43:17, 25, 44:1-6
[7] Paul Parisi dep., 58:18-24
[8] ETH-18997-19057; ETH.MESH.02259836

Over the course of years, the Prolift was among a group of transvaginally placed polypropylene mesh devices that were the subject of FDA notifications in October 2008 and July 2011, professional society statements (AUA, SGS, SUFU) and AUGS/ACOG Committee Opinion 513, and FDA panel hearings in September 2011. Ethicon eventually advised the FDA in May 2012 that the Prolift would no longer be sold, rather than performing rigorous studies demanded by the FDA.[9] Ethicon also changed the indications for Gynemesh PS, to no longer be placed transvaginally.[10] Ultimately, the FDA re-classified the category of devices to which the Prolift belonged, determining they are high risk and must be rigorously studied for safety before they can be marketed.

I. Alternatives to the Prolift

The Prolift was developed as an alternative to the traditional methods of surgical treatment of pelvic organ prolapse. These alternatives are safer and medically superior to the Prolift.

Ethicon promoted the idea that the Prolift was needed due to "high" failure and recurrence rates with traditional surgery. Ethicon defined an unmet need as "something that physicians who do this type of surgery want to be able to achieve that they can't at that time."[11] The unmet need that Ethicon claimed needed to be met was, as stated in the global launch plan, "A standardized procedure for repair of cystocele, rectocele, and vaginal vault prolapse that is more effective and in some cases faster than the currently available procedures."[12]

The most prevalent surgical treatment of pelvic organ prolapse is traditional suture repair utilizing the patient's own tissue, strengthened by sutures. Although traditional suture repair has risks, these risks are less severe and more easily treated than the risks posed by the Prolift, and of course does not introduce any of the risks unique to the implantation or presence of the permanent Prolift polypropylene mesh. Moreover, the risks of traditional repairs are almost all reasonably treatable within a short period of time, in contrast to the untreatable and lifelong risks of the Prolift. In addition, where a recurrence of prolapse occurs, this can be retreated. Traditional suture repair remains a safer procedure for the treatment of pelvic organ prolapse, while offering comparable efficacy. As discussed in detail herein, Ethicon inaccurately cited to and summarized medical literature in order to support its marketing campaign, creating the false impression that the failure and recurrence rates of traditional surgery were far higher than they actually were.

A second alternative to the Prolift is sacrocolpopexy. When this procedure is performed through an open incision in the abdomen, it is referred to as abdominal sacrocolpopexy (ASC). Alternatively, it can be performed through laparoscopic incisions in the abdomen; some centers are able to perform this robotically. Sacrocolpopexy involves attachment of the vaginal vault, typically, to the sacrum; variations have been described in which the cervix or uterus are attached

[9] ETH.MESH.04005092-04005093.
[10] The change in the Gynemesh PS indications to only include abdominal placement is a clear admission that the use of Gynemesh PS through the vagina is not safe. ETH.MESH.04005088-04005089.
[11] Bonet dep., 129:24-130:2
[12] Bonet dep., 131:23-132:3

instead of the vagina. In some cases, the vagina can be attached to the sacrum directly with sutures; this requires that the vagina be long enough to perform this without tension. More commonly, biologic or synthetic graft is attached to the vaginal apex, which is then attached to the sacrum. Most published case series of sacral colpopexy report the use of synthetic graft or mesh used at the vaginal apex for attachment to the sacrum.

Sacrocolpopexy is commonly regarded as the "gold standard" for prolapse repair, particularly for recurrent vaginal vault or apical vaginal prolapse. The primary benefit of sacrocolpopexy is durable anatomic results. A systematic review reported that success rate, when defined as lack of apical prolapse, ranged from 78% to 100% and when defined as no postoperative prolapse in any compartment, the success rate ranged from 58% to 100% with follow-up from 6 months to 3 years.[13] The risks, as with implantation of any permanent mesh, include mesh-related complications. In this systematic review, mesh erosion occurred in 3.4% (70 to 2178 cases). Other risks are related to the abdominal approach; when sacrocolpopexy is performed abdominally (i.e., with an open laparotomy incision), gastrointestinal complications of small bowel obstruction that required reoperation occurred in 1.2% (4 of 322 patients) after surgery.[14]

Another alternative to the Prolift is the use of Gynemesh PS, cut by the surgeon to be used to augment traditional repair surgery. Although not advocated here as a safe alternative compared to the alternatives that do not involve the implantation of mesh through the vagina, this is clearly a safer and less morbid alternative to the Prolift system. For example, this avoids the use of the larger amount of mesh with the Prolift, avoids the external incisions and blind trocar passages, and avoids the introduction of permanent mesh and its subsequent complications to non-vaginal, non-pelvic areas of the body, including due to the arms. This less aggressive use of mesh would have been less lucrative for Ethicon. For example, the Prolift pre-launch Global pricing strategy stated as an objective: "To increase the value of the prolapse segment from the "cost" of a piece of mesh $60 to the cost of a value added procedure ($1,000)."[15] At least one respected pelvic floor surgeon, Dr. Raz, has commented on this issue, in the broader context of criticizing the use of transvaginal mesh repair kits.[16]

In this context it was known to Ethicon that "key opinion leaders and very respected physicians in the field" would not use the Prolift "because they didn't feel that it was safe and efficacious enough to justify the risks of using mesh through that method."[17] Yet, Ethicon chose to commercially market the Prolift despite the considered opinions of many respected surgeons (with no financial bias) that it was not proven safe and effective. An additional alternative available to Ethicon was the use of Ultrapro mesh rather than Gynemesh PS mesh for the Prolift Systems, as eventually was done in creating the Prolift +M Systems (discussed below).

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[13] PLTMEDLIT00786: Nygaard IE et al. Abdominal sacrocolpopexy: a comprehensive review. Obstet Gynecol Oct. 2004; 104: 805-823.
[14] Whitehead WE et al. Gastrointestinal complications following abdominal sacrocolpopexy for advanced pelvic organ prolapse. Am J Obstet Gynecol 2007; 197:78.e1-7.
[15] ETH.MESH.00129533.
[16] Using mesh to repair prolapse calls for more than a kit – it takes skill; OBG Mangement, Vol. 21, No. 1, January, 2009.
[17] Jones dep., 724:3-11

The Prolift Systems introduce numerous risks not present with alternative procedures for treatment of pelvic organ prolapse and unreasonably increase the risks of complications that are intrinsic to pelvic organ prolapse surgery in general. It is important to recognize that the treatment of complications following non-mesh, non-trocar based surgery is usually straightforward, whereas treatment of complications following Prolift surgery presents significant complexities, and in many cases, invasive treatment and multiple operations cannot successfully treat Prolift-related complications, leaving patients with permanent, life-altering injuries. Thus the Prolift was medically unsafe, with an unacceptable and unnecessary risk benefit profile.

II. The Development of the Prolift

In the 1990's, physicians began to experiment with the use of Prolene and other hernia meshes off-label to augment the surgical repair of pelvic organ prolapse. Ethicon then developed a "lighter" polypropylene mesh product called Prolene Soft mesh, also for use in hernia repair. Prolene Soft mesh was also used experimentally by physicians off-label in the surgical repair of pelvic organ prolapse. Ethicon recognized this marketing opportunity and sought and obtained 510(k) clearance to legally market Prolene Soft mesh under the trade name of Gynemesh PS mesh, indicated for use in surgery for pelvic organ prolapse, on January 10, 2002.

The French TVM group, beginning in about 2000, used meshes such as Prolene, Prolene Soft mesh, Vypro mesh, and ultimately Gynemesh PS mesh as they developed the TVM technique for the repair of pelvic floor defects. Ultimately, the work of the TVM group was sold or assigned to Ethicon, was refined by Ethicon, was renamed the Prolift technique, and was first marketed beginning on March 10, 2005. As confirmed by multiple Ethicon employees, the Prolift was not studied in any clinical study prior to launch.[18]

Despite the important difference in clinical indications and the markedly different surgical environment,[19] Ethicon performed no pre-clinical or clinical testing to determine how Gynemesh PS mesh would function when used in prolapse surgery.[20] Ethicon made several key assumptions underlying the conclusion that the Prolift would be safe and effective; however Ethicon had no compelling evidence to support these assumptions and, in some cases, had clear evidence that contradicted these assumptions. These assumptions included 1) the assumption that animal testing with Prolene sutures and mesh adequately represented the effect of Gynemesh PS mesh in the female pelvis such that further testing was not warranted; 2) the assumption that surgical conditions of hernia repair sufficiently resembled surgical conditions of prolapse repair, particularly transvaginal prolapse repair, such that further testing was not warranted; and 3) the assumption that the chemical equivalence of Prolene Soft mesh and Gynemesh PS mesh equated the same "clinical

[18] Giselle Bonet dep., 102:1-7
[19] ETH.MESH.00164607: "The vagina is NOT the abdomen (nor similar to any other surgical environment)"
[20] ETH.MESH.01160159, Gynemesh Prolene Soft mesh, pre-clinical functionality testing strategy, 11-1-2001, Conclusion: "Based upon the Gynemesh Prolene Soft mesh's product characteristics, intended clinical indications and the use of existing polymer materials, additional pre-clinical functionality testing is not required."

tissue compatibility" despite use in markedly different surgical conditions, such that further testing was not warranted.

It is important to understand the properties, function, and use of Gynemesh PS mesh to fully understand the Prolift Systems.

Gynemesh PS Mesh Construction

Gynemesh PS mesh is constructed of nonabsorbable polypropylene monofilaments that are knitted to form the mesh and is the same material as Prolene Soft hernia mesh. Although Ethicon marketed the Gynemesh PS mesh as having the design advantage of large pores, which would prevent the potentiation of infection,[21] this was misleading. The construction of Gynemesh PS mesh results in irregular pore geometries and size such that it is not accurate to report a distinct pore size.[22] Because the mesh is constructed as a knitted fabric, some spaces between filaments are very small,[23] and where the mesh filaments are crossed and intertwined, referred to as interstices, there is no true "space" at all. Thus, the mesh can harbor bacteria yet exclude macrophages, thereby increasing the risk for mesh complications including exposure, erosion, and infection, compared with meshes constructed with consistently large pores.[24]

Gynemesh PS Mesh Density

The Gynemesh PS mesh is considered of medium density,[25] compared with meshes of higher density such as Prolene mesh

Cutting of Gynemesh PS Mesh

The Gynemesh PS mesh is ultrasonically cut.

Shape of Gynemesh PS Mesh

The shape of Gynemesh PS mesh is rectangular, and it is sold by Ethicon as single sheets in two sizes, 25 × 25 cm and 10 × 15 cm.

Surgery Using Gynemesh PS Mesh

Permanent synthetic meshes, including Gynemesh PS mesh, have traditionally been used in pelvic organ prolapse surgery when performed abdominally, typically during abdominal sacral

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[21] ETH-00253, Gynecare Gynemesh* PS Nonabsorbable Prolene* Soft Mesh, advertising material. Copyright dated 2006. Statement that "Knitted monofilament does not potentiate infection" with citation of Iglesia CB, Fenner DE, Brubaker L. The use of mesh in gynecologic surgery. Int Urogynecol J 1997; 8: 105-115. However, the citation does not support the advertising claim. The only statement regarding Prolene and infection is as follows: "Polypropylene mesh (Marlex, Prolene, Atrium) is a strong, non-absorbable monofilament material that is highly elastic and able to withstand infection."

[22] ETH-83452: 6-14-2006 - Robert Rosseau: "Pore size in microns was not measured during the development of the Prolene Soft Mesh. The total percent area that is open was measured and is considered an accurate method. Since the product construction results in irregular pore geometries and size, it is not accurate to report a distinct pore size."

[23] ETH-83788: 1-26-2006 - Range of pore sizes (mm^2) in Prolene Soft mesh: 0.29, 0.34, 1.08, 1.29, 1.70, 2.38

[24] Pore size is an important determinant of the risk of infection after synthetic mesh placement. Bacteria average 1 micron in size, and infection-fighting white blood cells (macrophages, granulocytes) are larger than 50 microns in size. Meshes classified as Type I, totally macroporous meshes, are constructed such that ALL mesh interstices, in each of their three dimensions, are larger than 75 microns. Therefore, "average" pore size is irrelevant to the risk of infection after synthetic mesh placement; the size of the SMALLEST pores is the critically important characteristic. [Amid PK. Classification of biomaterials and their related complications in abdominal wall hernia surgery. Hernia 1997; 1:15-21.]

[25] ETH-70366: unit weight of Gynemesh PS mesh = 4.5 ± 0.3 mg/cm^2

colpopexy (open or laparoscopic). When permanent synthetic mesh is used in abdominal sacral colpopexy, mesh erosion has been reported to occur in approximately 3% of patients.[26] However, when vaginal contamination occurs in the setting of abdominal use of permanent mesh, the frequency of mesh erosion increases dramatically.[27]

Gynemesh PS mesh has been used to perform vaginal prolapse repair, as an adjunct placed over traditional colporrhaphy[28] and/or placed in a "tension-free" manner, either in the surgical spaces created by dissection with or without suture attachment to pelvic structures[29] or by passing mesh straps through pelvic structures as a forerunner to the TVM technique.[30]

Product Development of Gynemesh PS Mesh

On November 6, 2001, Ethicon submitted a premarket notification application K013718 to the FDA for Gynecare Gynemesh PS Prolene Soft mesh.[31] Ethicon cited predicate devices of Prolene Soft mesh (of the same construction as Gynemesh PS mesh), Prolene mesh, and Mersilene mesh. On January 8, 2002, the FDA cleared Gynemesh PS mesh to be legally marketed, indicated for use in prolapse surgery.[32]

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[26] In a comprehensive review, Nygaard IE et al reported mesh erosion in 3.4% (70 of 2178 cases) (Nygaard IE et al. Abdominal sacrocolpopexy: a comprehensive review. Obstet Gynecol Oct 2004; 104: 805-823; PLTMEDLIT-00786).

[27] In a 2001 study of different abdominal prolapse repair techniques by Visco AG et al, mesh erosion occurred in 3.2% (5 of 155 cases) of standard abdominal sacral colpopexy. However, in abdominal sacral colpoperineopexy when mesh-anchoring suture was placed into the perineal body from the abdominal approach, mesh erosion occurred in a higher proportion of cases, 4.5% (5 of 88 cases). In abdominal sacral colpoperineopexy when mesh-anchoring suture was placed into the perineal body from the vaginal approach, mesh erosion occurred in 16% (4 of 25 cases); and in abdominal sacral colpoperineopexy when the mesh itself was placed from the vaginal approach, mesh erosion occurred in 40% (2 of 5 cases) (Visco AG et al. Vaginal mesh erosion after abdominal sacral colpopexy. Am J Obstet Gynecol 2001; 184:297-302; PLTMEDLIT-00623).

[28] Milani R et al. Functional and anatomical outcome of anterior and posterior vaginal prolapse repair with prolene mesh. BJOG Jan 2005; 112: 107-111.

Deffieux X et al. Vaginal mesh erosion after transvaginal repair of cystocele using Gynemesh or Gynemesh-Soft in 138 women: a comparative study. Int Urogynecol J 2007 Jan; 18: (1): 73-79. Epub 2006 Jan 4.

[29] ETH-60142: de Tayrac R et al. Tension-free polypropylene mesh for vaginal repair of anterior vaginal wall prolapse. J Reprod Med Feb 2005; 50: 75-80.

ETH-76140: de Tayrac R et al. A 2-year anatomical and functional assessment of transvaginal rectocele repair using a polypropylene mesh. Int Urogynecol J 2006; 17: 100-105. Epub 21 May 2005.

ETH-02813: de Tayrac R et al. Long-term anatomical and functional assessment of trans-vaginal cystocele repair using a tension-free polypropylene mesh. Int Urogynecol J 2006; 17: 483-488. Epub 17 December 2005.

ETH-76690: Natale F et al. A prospective randomized controlled study comparing Gynemesh, a synthetic mesh, and Pelvicol, a biologic graft, in the surgical treatment of recurrent cystocele. Int Urogynecol J 2009; 20: 75-81. Epub 16 Oct 2008.

ETH-76182: Ganj FA et al. Complications of transvaginal monofilament polypropylene mesh in pelvic organ prolapse repair. Int Urogynecol J 2009; Epub April 7 2009.

ETH-76774: Carey M et al. Vaginal repair with mesh versus colporrhaphy for prolapse: a randomized controlled trial. BJOG 2009. Epub 7 July 2009.

[30] ETH-02794: Collinet P et al. Transvaginal mesh technique for pelvic organ prolapse repair: mesh exposure management and risk factors. Int Urogynecol J 2006 Jun; 17(4): 315-320. Epub 2005 Oct 15.

[31] ETH-00797-00927

[32] ETH-07304-07310, FDA clearance letter for Gynemesh PS mesh, with this indications statement: "GYNEMESH PROLENE Soft (Polypropylene) Mesh is indicated for tissue reinforcement and long-lasting stabilization of fascial structures of the pelvic floor in vaginal wall prolapse where surgical treatment is intended, either as mechanical support or bridging material for the fascial defect."

No Specific Training or Procedure for Gynemesh PS Mesh

Gynemesh PS mesh is sold only as a surgical mesh, and no specific training or insertion procedure is recommended by Ethicon for the use of Gynemesh PS mesh.

Although no specific training or technique is recommended for the use of Gynemesh PS mesh, Ethicon sponsored national and international marketing-driven workshops with regard to Gynemesh PS mesh. Ethicon had 2 marketing-driven goals in offering these Gynemesh PS mesh workshops: (1) to convert surgeons to mesh prolapse repairs from non-mesh prolapse repairs; and (2) to enlarge the pool of surgeons who would become users of the Prolift procedures.[33]

Marketing of Gynemesh PS Mesh

Gynemesh PS mesh was marketed as an innovative product designed for the treatment of POP, even though it was not specifically designed for prolapse surgery. In actuality, Gynemesh PS mesh is the same mesh as Prolene Soft mesh, developed for and marketed by Ethicon to general surgeons for hernia repair. Gynemesh PS mesh was simply renamed to distinguish it from Prolene Soft mesh. Ethicon attempted to create a distinction between Prolene Soft mesh and Gynemesh PS mesh in three ways.

(a) Change in Indications Statement

In May 2000, Ethicon received FDA clearance to market Prolene Soft mesh, indicated for the repair of hernia or other fascial defects.[34] In January 2002, Ethicon received FDA clearance to market Gynemesh PS mesh, the exact same mesh as Prolene Soft mesh, now indicated for vaginal wall prolapse repair.[35]

(b) Sales Strategy

Ethicon instructed its sales representatives to sell the two products, Prolene Soft mesh and Gynemesh PS mesh, to different markets. Sales staff representing Prolene Soft mesh focused on general surgeons and their use of mesh for hernia repair. Sales staff representing Gynemesh PS

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[33] 3-24-2005, ETH-60149, Email from Greg Prine: "One of our biggest challenges moving forward will be our ability to clearly communicate with our physicians how to use Gynemesh tension free in POP procedures. This will also help to ensure a healthy pipeline of targets for Prolift moving forward. This information should be helpful in shorten [sic] the learning curve with your physicians that are just starting to use mesh. We need to prepare our future Prolift users, today."

9-21-2004, ETH-60136, Email from Marianne Kaminski, regarding GYNEMESH PS professional education training: "We have additional budget for GYNEMESH PS 'market seeding' via PE courses !!!!! Giselle has allocated $26,700 to Each Region. Goal - Conduct GYNEMESH PS training to prepared [sic] key customers to successfully adopt the next generation pelvic floor product in Q1, by adopting GYNEMESH PS now."

10-7-2004, ETH-60136, Email from Giselle Bonet: "It is critical that we expand our user base of Gynemesh this year so that we can have a successful launch of our next generation pelvic floor product in Q1."

[34] Prolene Soft mesh: Letter from FDA, dated May 23, 2000: K001122. Indications for Use: The Prolene soft (polypropylene) mesh is indicated for the repair of hernia or other fascial defects that require the addition of a reinforcing or bridging material to obtain the desired surgical result.

[35] Gynemesh PS mesh: Letter from FDA, dated January 8, 2002: K013718. Indications for Use: GYNEMESH PROLENE Soft (Polypropylene) Mesh is indicated for tissue reinforcement and long-lasting stabilization of fascial structures of the pelvic floor in vaginal wall prolapse where surgical treatment is intended, either as mechanical support or bridging material for the fascial defect.

mesh focused on gynecologists, urologists, and urogynecologists and their use of the mesh for pelvic organ prolapse repair.[36]

(c) Marketing of Gynemesh PS

Ethicon marketed the Gynemesh PS mesh as if it were uniquely designed to meet the needs of pelvic organ prolapse repair surgery.[37] This was incorrect since Prolene Soft mesh was developed for use in hernia repair.

III. Description of the Prolift Systems Mesh and Instruments

The Prolift Systems consist of pre-cut, pre-shaped Gynemesh PS mesh implants and three sets of single-use instruments (guide, cannulas, and retrieval devices) for mesh implant placement, via the Prolift procedure.[38] There are 3 different Prolift Pelvic Floor Repair Systems: Total, Anterior, and Posterior.

The components of the Prolift Systems are used to perform vaginal surgery for the treatment of pelvic organ prolapse. Briefly, vaginal and skin incisions are made, and vaginal dissection performed. The guide is inserted into one of the cannulas, and the guide-cannula combination (trocar) is blindly inserted from one of the skin incisions, through the pelvic tissues, and into one of the vaginal incisions. The guide is removed from the cannula, and one of the straps of the mesh implant is fed through the cannula and retrieved using one of the retrieval devices. These steps are repeated until all cannulas and straps of the mesh implant have been placed. The cannulas are removed, excess mesh is trimmed from the straps of the mesh implant at the skin incisions, and the vaginal and skin incisions are closed. See below for a more detailed description of the Prolift components, instruments, contents, and procedures.

Components of the Prolift Systems

Mesh Implants

The mesh in the Prolift Systems is the same as Gynemesh PS mesh, except that the Prolift mesh is laser-cut, rather than ultrasonically cut as the Gynemesh PS mesh is. The Prolift mesh implants are precut in complex shapes, with a central body and 6, 4, or 2 straps, depending on the type of the Prolift System, Total, Anterior, or Posterior, respectively.

Mesh Implant in the Prolift Total System

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[36] ETH-60102: Memo to all ETHICON PRODUCTS Field Sales Associates and all GYNECARE Field Sales Associates, May 14, 2003: "From a sales direction standpoint, we want to be clear. The ETHICON Products sales group will focus their efforts on promoting the benefits of PROLENE Soft for use in hernia and abdominal wall repair, targeting general surgery. The GYNECARE sales group will focus on promoting GYNEMESH PS for pelvic floor repairs to gynecologic, urogynecologic and urologic surgeons."

[37] Advertising content of Gynemesh PS mesh:
ETH-00252: "Technologically Advanced by Design – Driven by Innovation"
ETH-00253: "Unique Permanent Material for Durable Solutions"

[38] Prolift IFU, ETH.MESH.02341522; Prolift surgical technique document, ETH.MESH.00419571

The mesh implant in the Prolift Total System has a large central body with 6 straps, 4 for securing the anterior portion of the implant via a transobturator approach and 2 for securing the posterior portion of the implant in the sacrospinous ligament by a transgluteal approach or a vaginal approach. The surface area of the mesh in the Prolift Total System is 54.1 inches squared.[39]

Mesh Implant in the Prolift Anterior System

The mesh implant in the Prolift Anterior System has a central body with 4 straps for securing the implant via a transobturator approach. The surface area of the mesh in the Prolift Anterior System is 42.3 inches squared.[40]

Mesh Implant in the Prolift Posterior System

The mesh implant in the Prolift Posterior System has a central body with 2 straps that are secured in the sacrospinous ligament via a transgluteal approach or a vaginal approach. The surface area of the mesh in the Prolift Posterior Repair System is 24.7 inches squared.[41]

Instruments

Guide

The Prolift Guide is a sharp single-patient-use instrument designed to create tissue paths to allow placement of the mesh implants and to facilitate placement of the Prolift Cannula. The Prolift Guide is also described as a trocar.

Cannulas

The Prolift Cannula is a single-patient-use instrument designed to be used in conjunction with the Prolift Guide to facilitate passage of the implant straps while protecting the surrounding tissue. Each Prolift Cannula is placed over the Prolift Guide before passage and remains in place after the Prolift Guide is withdrawn.

Retrieval Devices

The Prolift Retrieval Device is a single-patient-use instrument designed to facilitate placement of the Prolift mesh implant straps. The Prolift Retrieval Device is passed through the previously positioned Prolift Cannula until its distal end is retrieved through the vaginal dissection. The distal end of the Prolift Retrieval Device has a loop to capture the mesh implant strap as the strap is drawn out through the Prolift Cannula.

Contents of the Prolift Pelvic Floor Repair Systems Kits

Prolift Total System

The Prolift Total System includes the total mesh implant, the retrieval guide, 6 cannulas, and 6 retrieval devices.

[39] ETH-70371
[40] ETH-70371
[41] ETH-70371

Prolift Anterior System

The Prolift Anterior System includes the anterior mesh implant, the retrieval guide, 4 cannulas, and 4 retrieval devices.

Prolift Posterior System

The Prolift Posterior System includes the posterior mesh implant, the retrieval guide, 2 cannulas, and 2 retrieval devices.

IV. The Assessments of the Design and Performance of the Prolift Before Marketing

Ethicon was required to establish and conduct robust assessments of the Prolift before the Prolift Systems could be marketed. Based on the criteria utilized by Ethicon in this assessment process, the assessments were inadequately performed, and the resulting conclusion that the Prolift could be marketed as a safe and effective medical device system was incorrect. This opinion is based upon analysis, from a medical perspective, of the evaluation by the medical affairs director who was tasked with this responsibility, Charlotte Owens, and the failure by the succeeding medical directors to remedy these medical evaluation flaws.

The Prelaunch Assessment of Risks and Complications For the Prolift

FDA Design Control Guidance

Pursuant to FDA regulation, a medical device manufacturer must conduct a design assessment to ensure that the device is safe and effective. This requirement is described in the FDA publication titled: "Design Control Guidance for Medical Device Manufacturers – The Guidance related to FDA 21 CFR 820.30 and sub-clause 4.4 of the ISO 9001." The purpose and requirements of this standard are intended to "ensure good quality assurance practices," and to act as a system of "checks and balances." [42],.[43]

Ethicon's Pre-Launch Design Control

Accordingly, before the launch and marketing of any medical device, including the Prolift, Ethicon performed an internal assessment to medically evaluate the potential risks/complications/adverse events, and whether these could be mitigated (prevented or minimized) by warnings/instructions or design changes. Piet Hinoul confirmed that the primary components of the prelaunch assessment, the device design safety assessment ("DDSA"), the application failure modes and effects analysis ("aFMEA"), and design failure modes and effects analysis ("dFMEA") are intended to capture all the possible things that can go wrong and how they are going to mitigate

[42] Design Control Guideline for Medical Device Manufacturers, p.i, 1-5, 8, 17, 23, 29, 34, 43

[43] As described below, Ethicon failed to properly monitor and act upon the demonstrated lack of safety and effectiveness following the launch of the Prolift.

those risks, or in other words to "make sure you capture all the things that can go wrong so that you make sure you assess all the potential complications."[44]

In the case of potential serious complications that can foreseeably occur with the Prolift, which could not be mitigated, Medical Affairs was required to assess whether the potential benefit of the Prolift outweighed the inevitable serious complications. This final assessment was based on the "judgment" of those in Medical Affairs.[45]

Scott Ciarocca, the research and development project leader for the Prolift project, testified that it was medical affairs who identified the hazards to be evaluated..[46] Scott Ciarocca also confirmed that the identification of all known hazards by medical affairs was essential to be able to use the DDSA as intended..[47]

The FMEA Procedure (OP650-011, Revision 6)[48]

Pursuant to the Design Control Guidance, Ethicon established a procedure to be followed in conducting the FMEAs. Jeffrey Everett confirmed that this procedure was utilized for the Prolift. This is the FMEA analysis that is required as part of the DDSA as stated above. With regard to identification of potential hazards and harms as a result of failure modes, and the occurrence frequencies that should be assigned, those questions certainly do fall within my expertise, and I can state unequivocally that those aspects of the analysis were inadequate and provided a misleading evaluation of the Prolift, which vastly understated the level of risk posed by the Prolift.

The final version of the aFMEA for the Prolift is dated March 2, 2005,[49] and the dFMEA is dated March 1, 2005,[50] both conducted pursuant to Procedure number OP650-011, version 6.[51] According to the Procedure, the FMEA is defined as **"A methodology for evaluating and analyzing risks resulting from potential failure modes, with the objective of eliminating or minimizing these risks to an acceptable level with the current state of technology."** The dFMEA focuses "on the design's ability to function reliably within the intended functional parameters," and the aFMEA focuses "on the design application, with the aim of identifying, eliminating, or minimizing the impact of potential risks associated with the user, user-interface, or human factor events."[52] In performing the aFMEA, Ethicon assumed that the Prolift was "delivered to the user in a state that it meets all of the requirements that are defined for it in its design and

[44] Hinoul Dep., 365:8-366:7, 375:18-22, 420:11-421:4.
:[45] Hinoul dep., 367:13-369:24.
[46] Scott Ciarocca dep., 339:6-24
[47] Scott Ciarocca dep., 342:16-343:3
[48] ETH.MESH.03742864-03742891
[49] ETH-07248-07303
[50] ETH-03569-03578
[51] ETH.MESH.03742864-03742891
[52] ETH.MESH.03742866

marketing specifications."[53] In defining potential failure modes (the ways the medical device in conjunction with the user can fail to perform the desired function), Ethicon also assumed "that the medical device is being used as intended or is being used in a manner that is reasonably expected (even if not intended.)"[54] Scott Ciarocca confirmed that this means "The user has read, comprehended, and followed the instructions for use in the IFU," and "the user completed the professional education as recommended by the IFU for Prolift,"[55] citing the memo with the final aFMEA.[56]

Medical Flaws In The DDSA and FMEA'S

Piet Hinoul agreed that the DDSA and FMEA's would be flawed if they "did not capture all of the potential complications, that would at least to that extent create a flaw in the DDSA [and FMEA's] assessment because it would be incomplete," and also "if an adverse event serious complication should have been included because it was known to Medical Affairs but was not included, that would flaw the DDSA [and FMEA's] to that extent, to the extent it was left out of the assessment."[57]

Scott Ciarrocca, who was the research and development project leader for the Prolift project, also testified to the critical importance of capturing all potential failure modes, hazards, and harms in the FMEA analysis in order to ensure that a valid assessment is performed. Mr. Ciarocca specifically testified as follows.[58] This testimony confirms that if failure modes and risks that should have been anticipated were not, then the FMEA is not "valid." [59]

The ultimate goal of the prelaunch assessments is to protect the health and safety of patients, the women who would have the Prolift implanted in their bodies. Without clearance of the Prolift through the DDSA and FMEAs, the Prolift could not obtain the final clearance to be marketed, known as Product Release Authorization (PRA). As stated by Scott Ciarocca, "When they put it on the market, we're certifying that it's safe and effective."[60] Based on Ethicon's own standards, created pursuant to the FDA design control regulation, the DDSA and FMEAs, as conducted, were flawed and thus could not serve as valid assessments to confirm the safety and effectiveness of the Prolift. These assessments failed to evaluate numerous significant risks/complications/adverse events, otherwise technically described as failure modes, hazards, and harms. The list of Hazards is incomplete. For example, Scott Ciarocca admitted to the failure by medical affairs to include a litany of hazards that could result from use of the Prolift:

> Q. Do you see listed in the list of hazards anything to do with chronic postoperative pain? Is that a hazard that's assessed?

[53] ETH.MESH.03742869
[54] ETH.MESH.03742881
[55] Scott Ciarocca dep., 563:21-564:10
[56] ETH-07248
[57] Piet Hinoul dep., 375:23-376:24.
[58] Scott Ciarrocca dep., 498:3-16, 500:5-10; 619:23-620:3
[59] Ciarrocca dep., 616:7-23; 617:22-618:7
[60] Scott Ciarrocca dep., 555:24-556:1

A. I do not see that in this table.

Q. How about dyspareunia, is that addressed as a potential hazard?

A. I do not see dyspareunia on this table.

Q. How about shrinkage or contraction of the mesh postoperatively, is that listed as a potential hazard?

A. I do not see that listed.

Q. How about inability to engage in comfortable or pleasurable sexual relations, is that listed as a potential hazard?

A. Dyspareunia?

Q. Well, whether it's due to pain or due to other factors, is there any –

A. I do not see that listed.

Q. What I was going to say, is there any hazard listed which would encompass painful sexual relations or difficult sexual relations in any way. There's nothing there. Right?

A. I do not see anything.

The admitted failure to evaluate severe complications including chronic pain, dyspareunia, and difficult sexual relations, and shrinkage/contraction of the mesh, is a glaring omission by medical affairs. Moreover, the DDSA failed to include any complications due to the blind passage of Prolift trocars and permanent Prolift mesh implantation in non-vaginal, non-pelvic structures that cause complications in previously healthy areas, including the hip, thigh, and groin, that were uninvolved with the primary prolapse process. According to Scott Ciarrocca's testimony and the terms of the DDSA procedure, these and other omissions that can be identified invalidate the DDSA.

Scott Ciarrocca testified at length about the risks of chronic pain due to the insertion of a Prolift, and admitted explicitly, "chronic pain was not one of the elements that was looked at in the DDSA." Despite the fact that chronic pain could not be designed out as a risk, Scott Ciarrocca could not recall that anybody on the design team suggested that the risk of chronic pain was too significant to deem the Prolift safe.[61] This risk alone, if properly considered by medical affairs, should have resulted in finding that the Prolift was not "safe enough to be put on the market." The same holds true for contraction of mesh and the inevitable and untreatable consequences for many

[61] Scott Ciarrocca dep., 505:19-509:19

women.[62] Another glaring omission in the design process was the failure by Ethicon to study and address whether or to what extent Prolift complications could be safely and effectively treated. Scott Ciarrocca admitted this issue was not addressed.[63]

Ethicon had an obligation to medically evaluate all of the potential complications and their consequences, and to recognize that the Prolift was not safe if the data did not support a finding that the Prolift was safe. Ethicon failed to satisfy that obligation, for example, by failing to thoroughly study the grave consequences of trying to treat many mesh complications, and failed to recognize or admit that the Prolift introduced too much risk and was too unsafe to be marketed.

The hazards and harms addressed in the aFMEA and dFMEA are also inadequate. The FMEAs had significant omissions. Since every risk of the Prolift was known at launch,[64] all should have been evaluated in the DDSA and FMEAs. For example, addressing Prolift mesh contraction/retractions/shrinkage, Piet Hinoul confirmed that Medical Affairs was aware that "significant retraction could occur" with the Prolift, and this could result in pain, recurrent prolapse, vaginal mesh exposure, dyspareunia, the need to have subsequent invasive operations to try to either remove or revise the contracted Prolift mesh, and the need for multiple operations in an effort to treat those complications.[65] Despite this knowledge, this risk was not evaluated in the DDSA and FMEAs. The same occurred with regard to the foreign body reaction and chronic inflammatory process that was triggered by permanent Prolift mesh implantation. As set forth above, the clinical consequences (symptoms), the need for surgical treatment, and the difficulty, if not impossibility, of treating these injuries were ignored as well in the DDSA and FMEAs. In addition, the DDSA and FMEAs failed to include complications caused by blind trocar passage and permanent Prolift mesh implantation in previously healthy areas of the body, including the hip, thigh, and groin, that were uninvolved in the primary process of prolapse.

The Prolift Did Not Satisfy The Design Requirements

An additional aspect of the assessment of the Prolift was the Design Requirements Matrix for the Prolift. This sets forth requirements to be satisfied so that the Prolift will function as intended, according to Scott Ciarrocca.[66] Scott Ciarrocca confirmed: "If during the course of development, the design was found not to meet a design requirement, then it would not be marketed."[67] In point of fact, the Prolift did not meet numerous Design Requirements and thus never should have been marketed.

[62] Scott Ciarrocca dep., 509:23-512:1
[63] Scott Ciarocca dep., 450:3-451:3
[64] Piet Hinoul deposition testimony, 480:8-13: "Q. As you sit here now, are there any risks or adverse reactions, adverse events connected to the Prolift that medical affairs at Ethicon knows of that were not known at the time of launch? A. No. So there are no new adverse events that we weren't aware of at the time of launch."
[65] Piet Hinoul deposition testimony, pages 22-23
[66] Scott Ciarrocca dep., 132:17-134:17
[67] Scott Ciarrocca dep., 357:2-10

The Design Requirements Matrix for the Prolift mesh implant, dated February 17, 2005, included numerous requirements.[68] The Design Requirements Matrix for the Prolift Guide, Cannula, and Retrieval Device, dated February 17, 2005, also included numerous requirements.[69]

The Clinical Expert Report

The approach to and analysis of design requirements (and the DDSA) was also flawed for yet another reason. One of the design requirements set forth in the design requirements matrix for the Prolift was that there must be clinical evidence supporting the safety and effectiveness of the Prolift. Scott Ciarrocca testified that he confirmed that this clinical evidence existed and checked off that requirement within the DDSA, based upon the existence of clinical data in the final signed version of Charlotte Owens' Clinical Expert Report for the Prolift dated January 14, 2005. Dr. Owens, the medical affairs director, was tasked with performing a purely medical function in assessing clinical evidence including medical literature to determine whether the risk benefit profile for the Prolift was safe. Specifically, Mr. Ciarrocca relied on section 4 of that report titled "Clinical Evidence."[70]

As described above, the first version of the clinical expert report drafted by Charlotte Owens recognized that clinical evidence was needed to establish the Prolift to be safe and effective, and that clinical study was needed in order to confirm this. However, as set forth, following input from Sean O'Bryan from Regulatory Affairs, and perhaps others, Charlotte Owens set aside her initial opinion, and then essentially copied the Gynemesh PS clinical expert report from almost 3 years prior, and passed that off as the clinical expert report applicable to the Prolift. The section relied upon by Scott Ciarrocca from the clinical expert report was copied almost verbatim from the Gynemesh PS clinical expert report, right down to certain typographical errors (i.e., prolaspe). Most important, no new research was summarized between the time that the Gynemesh PS clinical expert report was completed by Marty Weisberg on September 20, 2002, and the Prolift report was signed by Charlotte Owens as final on January 14, 2005. This is proven by the fact that the exact same articles are cited, with the exception of one reference that was removed from the Gynemesh PS clinical expert report, and one that was added with regard to the TVT device, and the glaring failure to cite to articles known to Ethicon, authored about the TVM procedure by the inventors. This includes a 2004 article by the TVM group discussing for example the serious risk of retraction, and that the procedure should only be indicated for advanced prolapse, and not for primary prolapse repair.[71] Marty Weisberg confirmed that it was improper if Charlotte Owens failed to independently research the issue.[72]

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[68] ETH.MESH.00308835-00308857
[69] ETH.MESH.00308858-00308891
[70] Ciarrocca dep., 360:8-363:23
[71] Possible explanations for the omission of relevant evidence between September 2002 and January 2005 are 1) Charlotte Owens either did no research at all in preparing the 2005 Prolift Clinical Expert Report; or 2) Charlotte Owens did do research but overlooked or ignored relevant publications between September 2002 and January 2005; and relevant presentations at national and international professional meetings between September 2002 and January 2005; and failed to include Ethicon's internal data regarding the French and US TVM studies.
[72] Marty Weisberg dep., 108:14-109:25.

Charlotte Owens was correct in her first draft of the Prolift clinical expert report in November 2004, when she admitted that clinical study was needed in order to attempt to prove the Prolift to be safe for use in humans. The information found in Section 4 of the Prolift clinical expert report does not provide clinical evidence establishing the safety and effectiveness of the Prolift. In fact, there was no clinical evidence with regard to the Prolift at the time the product was launched in March 2005 and, more than 2 years later in September 2007, Ethicon admitted to the FDA that no clinical studies had been performed on the Prolift Systems.[73] In addition, a fair and balanced review of the medical literature would have raised serious questions as to whether the Prolift could be expected to be safe or effective. The only responsible thing to do if Ethicon was determined to go forward and market the Prolift product for permanent Prolift mesh implantation in women would have been to NOT launch the Prolift in early 2005, but rather to initiate a closely monitored experimental clinical study, under strict supervision, and with an extensive informed consent, in order to learn about the performance of the Prolift in actual women.

V. The Prolift Procedure

The procedures performed using the Prolift Systems vary in significant ways from traditional pelvic floor repairs. In addition, despite claims made by Ethicon, the procedures performed using the Prolift Systems do not represent a straightforward extension from the use of the rectangular Gynemesh PS mesh implants as an adjunct to traditional pelvic floor repairs.

The surgical procedures using the Prolift Systems consist of a series of complex steps that vary depending on exactly what type of procedure is being performed. Twenty-six different procedures can be performed using the 3 different Prolift Systems, including 16 different procedures with the Prolift Total System; 2 different procedures with the Prolift Anterior System; 4 different procedures with the Prolift Posterior System; and 4 different procedures when the Prolift Anterior and Posterior Systems are used together.

The Prolift Total System can be used to perform 16 different procedures, depending on whether the patient has had a hysterectomy previously, and whether the surgery is performed with or without a concomitant hysterectomy, whether the total mesh implant is placed in one or two pieces, whether only anterior and apical repair is planned, and whether the posterior straps are placed using the transgluteal or vaginal approach.[74] When the Prolift Total procedure is performed

[73] ETH-00928-00939

[74] The Posterior Total System can be used to perform 16 different procedures, including:

(1) with a concomitant hysterectomy, using the transgluteal approach for the posterior straps, placing the total implant in one piece;

(2) with a concomitant hysterectomy, using the transgluteal approach for the posterior straps, placing the total implant in two pieces;

(3) with a concomitant hysterectomy, using sacrospinous fixation for the posterior straps, placing the total implant in one piece;

(4) with a concomitant hysterectomy, using sacrospinous fixation for the posterior straps, placing the total implant in two pieces;

using the transgluteal approach, the procedure includes 2 large vaginal incisions (each about 5-6 cm in length along the anterior and posterior vagina) and 6 small skin incisions (each about 4 mm in length; 2 in the obturator area and 1 in the gluteal area on the right and left sides of the patient). When the Prolift Total procedure is performed using sacrospinous fixation, the procedure includes 2 large vaginal incisions (each about 5-6 cm in length along the anterior and posterior vagina) and 4 small skin incisions (each about 4 mm in length, 2 in the obturator area on the right and left sides of the patient).

The Prolift Anterior System can be used to perform 2 different procedures, depending on whether the surgery is performed with or without a concomitant hysterectomy.[75] The Prolift Anterior procedure includes 1 large vaginal incision (about 5-6 cm in length along the anterior vagina) and 4 small skin incisions (each about 4 mm in length; 2 in the obturator area on the right and left sides of the patient).

The Prolift Posterior System can be used to perform 4 different procedures, depending on whether the surgery is performed with or without a concomitant hysterectomy and whether the

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(5) without a concomitant hysterectomy (uterine preservation), using the transgluteal approach for the posterior straps (it is necessary to place the total implant in two pieces);
(6) without a concomitant hysterectomy (uterine preservation), using sacrospinous fixation for the posterior straps (it is necessary to place the total implant in two pieces);
(7) in a patient with a previous hysterectomy, using the transgluteal approach for the posterior straps, placing the total implant in one piece;
(8) in a patient with a previous hysterectomy, using the transgluteal approach for the posterior straps, placing the total implant in two pieces;
(9) in a patient with a previous hysterectomy, using sacrospinous fixation for the posterior straps, placing the total implant in one piece;
(10) in a patient with a previous hysterectomy, using sacrospinous fixation for the posterior straps, placing the total implant in two pieces;
(11) with an anterior and apical repair only (no posterior repair) with a concomitant or previous hysterectomy, using the transgluteal approach for the posterior straps, placing the total implant in one piece;
(12) with an anterior and apical repair only (no posterior repair) with a concomitant or previous hysterectomy, using the transgluteal approach for the posterior straps, placing the total implant in two pieces;
(13) with an anterior and apical repair only (no posterior repair) with a concomitant or previous hysterectomy, using sacrospinous fixation for the posterior straps, placing the total implant in one piece;
(14) with an anterior and apical repair only (no posterior repair) with a concomitant or previous hysterectomy, using sacrospinous fixation for the posterior straps, placing the total implant in two pieces;
(15) with an anterior and apical repair only (no posterior repair) without a concomitant or previous hysterectomy (uterine preservation), using the transgluteal approach for the posterior straps (it is necessary to place the total implant in two pieces);
(16) with an anterior and apical repair only (no posterior repair) without a concomitant or previous hysterectomy (uterine preservation), using sacrospinous fixation for the posterior straps (it is necessary to place the total implant in two pieces).

[75] The Prolift Anterior System can be used to perform 2 different procedures, including:
(1) with a concomitant or previous hysterectomy; and
(2) without a concomitant hysterectomy (uterine preservation).

posterior straps are placed using the transgluteal or vaginal approach.[76] When the Prolift Posterior procedure is performed using the transgluteal approach, the procedure includes 1 large vaginal incision (about 5-6 cm in length along the posterior vagina) and 2 small skin incisions (each about 4 mm in length; 1 in the gluteal area on the right and left sides of the patient). When the Prolift Posterior procedure is performed using sacrospinous fixation, the procedure includes 1 large vaginal incision (about 5-6 cm in length along the posterior vagina).

When the Prolift Anterior and Posterior Systems are used together, 4 different procedures can be performed, depending on whether the surgery is performed with or without a concomitant hysterectomy and whether the posterior straps are placed using the transgluteal or vaginal approach.[77] When the Prolift Anterior and Posterior procedures are performed together with the transgluteal approach, the procedure includes 2 large vaginal incisions (each about 5-6 cm in length along the anterior and posterior vagina) and 6 small skin incisions (each about 4 mm in length; 2 in the obturator area and 1 in the gluteal area on the right and left sides of the patient). When the Prolift Anterior and Posterior procedures are performed together with sacrospinous fixation, the procedure includes 2 large vaginal incisions (each about 5-6 cm in length along the anterior and posterior vagina) and 4 small skin incisions (each about 4 mm in length; 2 in the obturator area on the right and left sides of the patient).

Details of the surgical techniques were obtained from the Prolift Systems Surgical Technique guide.[78]

Details of Problematic Prolift Procedural Steps

Blind passage of guides (trocars)

The Prolift procedure requires the unreasonable risk of the blind passage of trocars through multiple layers of pelvic tissues, without direct visualization of those structures and only with the surgeon's finger in the vaginal dissection to guide trocar passage. Blind passage of the Prolift trocars introduces significant and unreasonable risk to pelvic floor surgery, as it prevents the surgeon from being able to identify and avoid the vital neurovascular structures that are within and close to the operative field. It is important to note that palpation is not an equal or adequate substitute for visualization in this operative field. In addition, it is important to emphasize that an entirely new category of complications is introduced by blind trocar passage and permanent Prolift

[76] The Prolift Posterior System can be used to perform 4 different procedures, including:
(1) with a concomitant or previous hysterectomy, using the transgluteal approach;
(2) without a concomitant hysterectomy (uterine preservation), using the transgluteal approach;
(3) with a concomitant or previous hysterectomy, using sacrospinous fixation; and
(4) without a concomitant hysterectomy (uterine preservation), using sacrospinous fixation.

[77] The Prolift Anterior and Posterior Systems can be used to perform 4 different procedures, including:
(1) with a concomitant or previous hysterectomy, using the transgluteal approach;
(2) without a concomitant hysterectomy (uterine preservation), using the transgluteal approach;
(3) with a concomitant or previous hysterectomy, using sacrospinous fixation; and
(4) without a concomitant hysterectomy (uterine preservation), using sacrospinous fixation.

[78] ETH.MESH.00419571-00419600

mesh implantation in non-vaginal, non-pelvic structures, including the hip, thigh, and groin, that were previously unaffected and uninvolved in the primary process of prolapse.

Ethicon received feedback from experienced Prolift surgeons that the Prolift guide was too sharp, increasing the risk of damage to vital structures.[79] Ethicon also received feedback from participants in the Prolift Design Validation Study using cadavers, regarding difficulty in the placement and retrieval of the cannula-equipped guides in the Prolift procedure.[80,81] Nevertheless, the Prolift guide was not modified or removed from the kit, and the Prolift procedure was not modified to minimize or remove the unreasonably dangerous aspects of the procedure.

In recognition of the unreasonable risk of injury presented by the blind passages of the Prolift trocars, Ethicon developed an alternative pelvic mesh product to be placed only through the vagina, with no external skin incisions or blind trocar passages. This project was known as Project Neo, with an intended product name of Espriva.

The Prolift Total procedure requires the blind passage of 6 trocars, including 2 anterior superior trocars, 2 anterior inferior trocars, and 2 posterior trocars. The Prolift Anterior procedure requires the blind passage of 4 trocars, including 2 anterior superior trocars and 2 anterior inferior trocars. The Prolift Posterior procedure requires the blind passage of 2 trocars, the posterior trocars.

Dangers specific to the anterior trocar passes of the Prolift procedure

The Prolift surgical technique document states that the Prolift superficial anterior trocar should "pass through the obturator internus muscle approximately 1 cm from the proximal (prepubic) end of the ATFP [arcus tendineus fascia pelvis]."[82] The Prolift deep anterior trocar is placed "to emerge through the obturator internus muscle at the bottom of the paravesical fossa behind the ATFP, approximately 1 cm from the ischial spine."[83] In this way, "optimally, the anterior segment of the total [Prolift] implant will be positioned tension-free under the bladder while ensuring lateral contact against the ATFP."[84]

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[79] 11-23-2005, ETH-83323: suggestions from Pr. Jakob Eberhard on improvements to Prolift: "The guide is too sharp. This is unnecessary and presents a risk for the vessel or bowel perforation. A blunter guide would help to push away the surrounding tissue, rather than piercing it."

[80] 2-7-2005, ETH-01624, Prolift Design Validation, Comment: "Participant indicated that the ability for the cannula to facilitate user access to the retrieval device is poor." [Ethicon] response: "… during deep passages the tip of the cannula tended to get lost in deep tissues." In this context, "lost" means that the surgeon has to move the cannula around in the "deep tissue" of critical structures, including organs, arteries, veins, and nerves, while trying to retrieve the device. Damage caused by this maneuvering would not be evident in a cadaver.

[81] 2-7-2005, ETH-01626, Prolift Design Validation, Comment: "Entrance points were well defined but the exit points are not so clear." If the exit points of the cannula-equipped guides cannot be reproduced consistently, this increases the risk of damage to organs and major neurovascular structures in the pelvis and increases the risk of procedure failure if mesh is not secured correctly in the relevant supporting structures.

[82] ETH.MESH.00419576

[83] ETH.MESH.00491578

[84] ETH.MESH.00419584

There are two areas at highest risk due to blind passage of the 4 anterior Prolift trocars. The first area is at risk during initial placement of the 4 superficial and deep anterior Prolift trocars through the obturator foramina to exit the vaginal dissection on each side; during passage, these 4 trocars pass in close proximity to the obturator complex (vein, artery, and nerve), the bladder, and ureteral insertions into the bladder base. The 2 anterior superficial Prolift trocars pass through the skin incision, subcutaneous fat, gracilis muscle, adductor magnus muscle, obturator externus muscle, obturator membrane, and obturator internus muscle until they reach the proximal anterior vaginal dissection on each side. The 2 anterior superficial Prolift trocars pass within 5 mm of the bladder and within 6 mm of the medial branches of the obturator complex on each side.[85]

The two anterior deep Prolift trocars pass through the skin incision, subcutaneous fat, adductor magnus muscle, obturator externus muscle, obturator membrane, and obturator internus muscle until they reach the deep anterior vaginal dissection on each side. One study found that the 2 anterior deep Prolift trocars pass within 8 mm of the bladder and within 4 mm of the medial branches of the obturator complex on each side.[86] In another study, the 2 anterior deep Prolift trocars passed extremely close to the posterior division of the obturator vessels, the distance being only an average of 1.8 mm on the right and 1.1 mm on the left.[87] The obturator arteries and veins are of medium caliber.[88]

The second area is at risk during the passage of the 2 deep anterior Prolift trocars near the ischial spines to exit the deep anterior vaginal dissection on each side. As will be further discussed relative to passage of the posterior Prolift trocars, critical neurovascular structures are in close relation to the ischial spine, including the sciatic nerve, the pudendal complex (vein, artery, and nerve), and branches of the pudendal complex. The marked variation in the specific branching patterns of the neurovascular structures considerably complicates the avoidance of these neurovascular structures, particularly with blind passage of the 4 anterior Prolift trocars.[89] In addition, the rich blood supply in this area of the pelvis anastomoses freely with the vertebral, internal iliac, and external iliac arteriovenous systems, making it difficult to control blood loss with vascular injury.[90,91,92] If vascular injury occurs and is not detected intraoperatively, postoperative

[85] ETH-02601: Chen CCG et al. Anatomic relationships of the tension-free vaginal mesh trocars. Am J Obstet Gynecol Dec 2007; 197: 666.e1-e6.
[86] ETH-02601: Chen CCG et al. Anatomic relationships of the tension-free vaginal mesh trocars. Am J Obstet Gynecol Dec 2007; 197: 666.e1-e6.
[87] Touboul C et al. Perineal approach to vascular anatomy during transobturator cystocele repair. BJOG 2009; 116: 708-712. Epub 2009 Feb 4.
[88] Barksdale PA et al. An anatomic approach to pelvic hemorrhage during sacrospinous ligament fixation of the vaginal vault. Obstet Gynecol 1998; 91: 715-718.
[89] Ottem D, Stothers L. Transobturator tape: variation in the vascular anatomy of the obturator foramen. Can J Urol 2007; 14: 3678-3683.
[90] ETH-02334: Touboul C, Nizard J, Fauconnier A, Bader G. Major venous hemorrhagic complication during transvaginal cystocele repair using the transobturator approach. Obstet Gynecol 2008; 111: 492-495.
[91] Mokrzycki ML, Hampton BS. Pelvic arterial embolization in the setting of acute hemorrhage as a result of the anterior Prolift procedure. Int Urogynecol J 2007 Jul; 18 (7): 813-815. Epub 2006 Oct 5.
[92] Gangam N, Kanee A. Retroperitoneal hemorrhage after a vaginal mesh prolapse procedure. Obstet Gynecol 2007: 110: 463-464.

hematomas can develop and, indeed, often do after the Prolift procedure.[93] If a hematoma occurs in a contained space, bleeding may be self-limited,[94] and treatment can be conservative.[95,96] No doubt in some cases, a small hematoma may be asymptomatic and therefore undiagnosed. However, if a hematoma occurs in a space that allows for expansion under pressure, such as the retrovesical or retroperitoneal space, or in a free space, such as the peritoneal cavity, the situation can become life-threatening.[97,98] Required treatment may include transfusion,[99] drainage,[100,101] surgical exploration,[102] and/or radiologic embolization.[103,104] In addition, hematomas are a favorable environment for the development of abscesses, especially given the inevitable bacterial contamination with vaginal surgery.[105]

Several aspects of the anterior Prolift procedure introduce new and severe intraoperative risks that do not exist with traditional anterior vaginal prolapse repair. These include the obturator approach for Prolift mesh arm implantation, the relatively large caliber of the Prolift trocar in relation to the proximity of critical neurovascular structures and adjacent organs, and anterior Prolift mesh implantation that impinges on the bladder and ureteral insertions into the bladder base. In addition, the anterior Prolift procedure introduces new and severe postoperative risks that do not exist with traditional anterior vaginal prolapse repair, due to the permanent presence of the Prolift mesh implant in close proximity to the bladder, ureteral insertions into the bladder base, critical neurovascular structures, and previously uninvolved structures of the hip, thigh, and groin.

Traditional anterior vaginal prolapse repair, i.e., anterior colporrhaphy, is performed by dissecting the vaginal epithelium from the underlying muscularis layer and using stitches to plicate

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[93] Range from 1.1-5.0%; ETH-76015, ETH-75780, ETH.MESH.00004781, ETH.MESH.00306723, ETH.MESH.00829380

[94] Richards SR, Balaloski SP. Vulvar hematoma following a transobturator sling (TVT-O). Int Urogynecol J 2006; 17: 672-673.

[95] Anast JW et al. Pelvic hematoma following transobturator tape procedure: case report and review of the literature. Can J Urol 2008; 15: 3930-3932.

[96] Sun MJ et al. Obturator hematoma after the transobturator suburethral tape procedure. Obstet Gynecol 2006; 108 (3 Pt 2): 716-718.

[97] ETH-02634: Ignjatovic I, Stosic D. Retrovesical hematoma after anterior Prolift procedure for cystocele correction. Int Urogynecol J 2007; 18: 1495-1497.

[98] Gangam N, Kanee A. Retroperitoneal hemorrhage after a vaginal mesh prolapse procedure. Obstet Gynecol 2007: 110: 463-464.

[99] ETH-02660: LaSala CA, Schimpf MO. Occurrence of postoperative hematomas after prolapse repair using a mesh augmentation system. Obstet Gynecol 2007; 109: 569-572.

[100] ETH-02634: Ignjatovic I, Stosic D. Retrovesical hematoma after anterior Prolift procedure for cystocele correction. Int Urogynecol J 2007; 18: 1495-1497.

[101] Rajan S, Kohli N. Retropubic hematoma after transobturator sling procedure. Obstet Gynecol 2005; 106 (5 Pt 2): 1199-1202.

[102] Gangam N, Kanee A. Retroperitoneal hemorrhage after a vaginal mesh prolapse procedure. Obstet Gynecol 2007: 110: 463-464.

[103] ETH-03172: Mokrzycki ML, Hampton BS. Pelvic arterial embolization in the setting of acute hemorrhage as a result of the anterior Prolift procedure. Int Urogynecol J 2007 Jul; 18 (7): 813-815. Epub 2006 Oct 5.

[104] Muffly TM et al. Interventional radiologic treatment of pelvic hemorrhage after placement of mesh for pelvic reconstructive surgery. Obstet Gynecol 2012; 119 (2 Pt 2): 459-462.

[105] ETH-02660: LaSala CA, Schimpf MO. Occurrence of postoperative hematomas after prolapse repair using a mesh augmentation system. Obstet Gynecol 2007; 109: 569-572.

the muscularis layer over the bladder. In this way, the bladder is relatively protected since the vesicovaginal space is not opened, no deep structures are encountered, and blood loss is typically limited to that which occurs during dissection. In contrast, the anterior Prolift procedure requires passage of the 4 anterior Prolift trocars through areas of the pelvis, as described above, in close proximity to the bladder, ureters, and neurovascular structures. As discussed above, to minimize the morbidity incurred by the patient when bladder or ureteral injury occurs, it is critically important to detect and manage such injury intraoperatively. Nevertheless, Ethicon failed to inform surgeons of this critical need. Neither the original Prolift IFU nor the Prolift surgical technique document even mentioned cystoscopy to detect bladder and/or ureteral injury. Even after the Prolift IFU was revised to include cystoscopy as a suggestion (not a requirement), Ethicon failed to inform surgeons of the critically important issue of the timing of cystoscopy to detect bladder and/or ureteral injury BEFORE Prolift mesh implantation had taken place. Ethicon never revised the Prolift surgical technique document to address these issues.

As will be discussed below relative to passage of the posterior Prolift trocars as well, another aspect of the anterior Prolift procedure that introduces new and severe intraoperative risks that do not exist with traditional anterior vaginal prolapse repair is the relatively large caliber of the trocar in relation to the proximity of the bladder and neurovascular structures. The Prolift cannula-equipped guide (trocar) has a diameter of 4.5 mm.[106] As described above, the bladder is within 5 mm to 8 mm and the obturator complex is within 1 mm to 6 mm of the passage of the 4 anterior Prolift trocars. Therefore, the surgeon must blindly pass the 4.5-mm trocar at a sufficient distance to avoid injury to these nearby structures, while at the same time, pass the superficial anterior Prolift trocar within 1 cm of the prepubic end of the ATFP and pass the deep anterior Prolift trocar within 1 cm of the ischial spine.

Another aspect of the anterior Prolift procedure that introduces new and severe intraoperative risks that do not exist with traditional anterior vaginal prolapse repair is Prolift mesh implantation that impinges on the bladder and ureteral insertions into the bladder base. The anterior Prolift mesh body is implanted under the bladder, and the 4 anterior Prolift mesh arms on each side anchor the anterior Prolift mesh body by passing through the obturator foramina. Although the Prolift surgical technique document states that "optimally, the anterior segment of the total [Prolift] implant will be positioned tension-free under the bladder,"[107] Ethicon has acknowledged in deposition testimony that no mechanism exists to ensure "tension-free" Prolift mesh implantation. (See below). Anterior Prolift mesh implanted under tension can cause pore collapse, banding, contraction, pain, symptoms of obstructed voiding, and Prolift mesh erosion into the vagina and bladder. In addition, anterior Prolift mesh tension under the bladder impinges directly on the ureteral insertions into the bladder base. In fact, ureteral obstruction was described in one of the early case series of the Prolift procedure.[108] By intraoperative cystoscopy, no efflux was seen from one of the ureteral orifices; postoperative intravenous pyelogram showed ureteral obstruction, and

[106] ETH-03284: Cannula tubing shall have an OD [outer diameter] of 4.50 + 0.20 mm/-0.10 mm.
[107] ETH.MESH.00419584
[108] PLTMEDLIT01427: van Raalte HM, Lucente VR, Molden SM, Haff R, Murphy M. One-year anatomic and quality-of-life outcomes after the Prolift procedure for treatment of posthysterectomy prolapse. Am J Obstet Gynecol 2008; 199 (6): 694.e1-6.

the patient required reoperation to relieve the tension on the deep anterior Prolift mesh arm that was causing the obstruction.

However, Ethicon failed to advise that intraoperative cystoscopy was a necessary step to maximize patient safety and minimize the clinical impact of intraoperative complications from Prolift mesh implantation. If intraoperative cystoscopy had not been performed on the patient described above, the diagnosis of ureteral obstruction would have been at least delayed if not missed altogether, with the patient at risk for severe complications including eventual loss of renal function on that side. Moreover, Ethicon failed to advise surgeons about the risk of ureteral injury or obstruction during the Prolift procedure; the risk of ureteral injury or obstruction is never even mentioned in the original Prolift IFU, the revised Prolift IFU, or the Prolift surgical technique document. The revised Prolift IFU includes only a suggestion (not a requirement) that cystoscopy may be performed to detect "ureteral integrity."[109]

The anterior Prolift procedure also introduces new and severe postoperative risks that do not exist with traditional anterior vaginal prolapse surgery, including the permanent presence of the Prolift mesh implant in close proximity to the bladder and ureteral insertions into the bladder base and the neurovascular structures and the permanent presence of the Prolift mesh arms through the obturator foramina and exiting through the skin of the inguinal area. With traditional anterior vaginal prolapse repair, none of the deep structures are at risk. When anterior vaginal prolapse repair is augmented with non-trocar-based grafts, suture placement near the ischial spine can cause nerve or vascular injury. One case report described attachment of a biologic graft by suture placement near the ischial spine, resulting in neuralgia in the distribution of the pudendal nerve and perforating cutaneous nerve.[110] Suture removal 1 year after the index surgery resulted in 50% improvement of the patient's symptoms of pain, hypersensitivity, numbness, and dyspareunia. Regarding the risk of nerve injury, the authors recommended that "Sutures should be thoughtfully placed when anchoring a biologic graft or synthetic mesh to the proximal arcus tendineus fasciae pelvis, with care taken not to place the suture immediately adjacent to the ischial spine."

However, in the anterior Prolift procedure, anterior deep trocar passage and implantation of the anterior deep Prolift mesh arm is intended to pass within 1 cm of the ischial spine. Considering the 4.5-mm diameter of the trocar and the intended precision of blind passage of the anterior Prolift trocar, direct nerve injury or later nerve entrapment by the Prolift mesh is a distinct risk. The relative ease of suture removal stands in marked contrast to the difficulty or impossibility of removing the Prolift mesh encased in scarring and fibrosis without causing new significant morbidity and with less hope of symptom resolution.

Another aspect of the anterior Prolift procedure that introduces new and severe postoperative risks that do not exist with traditional anterior vaginal prolapse repair is the permanent presence of the Prolift mesh arms in the obturator foramina and exiting through the skin of the inguinal area. The permanent presence of the Prolift mesh arms incites a chronic

[109] ETH.MESH.02341734

[110] ETH-02311, Bohrer JC, Chen CCG, Walters MD. Pudendal neuropathy involving the perforating cutaneous nerve after cystocele repair with graft. Obstet Gynecol 2008; 112: 496-498.

inflammatory and foreign body reaction that may affect the bladder, ureteral insertions into the bladder base, and neurovascular structures. As the bilateral sets of anterior Prolift mesh arms retract as they pass near the bladder at 2 points on each side, along with retraction affecting the body of the anterior Prolift mesh itself, this retraction can tighten the Prolift mesh body that lies under the bladder, resulting in symptoms of obstructed voiding, ureteral obstruction, and Prolift mesh erosion into the bladder. With regard to the risk of delayed ureteral obstruction due to the Prolift mesh, this occurred in the earliest TVM studies.[111,112] This has also been reported in Prolift Issue Reports.[113] Ethicon failed to warn surgeons and patients about the risk of delayed ureteral obstruction after the Prolift procedure; the risk of delayed ureteral obstruction is never even mentioned in the original Prolift IFU, the revised Prolift IFU, or the Prolift surgical technique document. In addition, Ethicon failed to provide any guidance as to appropriate monitoring to detect delayed ureteral obstruction, and Ethicon failed to provide any guidance as to optimal means of management when delayed ureteral obstruction occurred after the Prolift procedure and permanent Prolift mesh implantation. These issues all illustrate the many unnecessary risks introduced to prolapse surgery by the Prolift.

Dangers specific to the posterior trocar passes of the Prolift procedure

The Prolift surgical technique document states that "the posterior segment (3) of the total [Prolift] implant is to be positioned in the ischioanal fossa, inferior to the levator ani muscle, and secured by passage of the straps through the sacrospinous ligament and coccygeus muscles [on each side]."[114] After dissection, this is accomplished by advancing the Prolift cannula-equipped guide "until it is in contact with the inferior side of the sacrospinous ligament approximately 3-4 cm medial to the ischial spine. It is then pushed through the sacrospinous ligament under digital control, thus exposing the tip of the guide and cannula."[115] The posterior passages introduce unreasonable risks, as recognized by Ethicon in the November 22, 2004 Prolift Overview of Kit Components, in discussing the Fastener System that was later not utilized. As stated, the "impetus" of the fastener was to "eliminate the posterior passage."[116]

[111] ETH-75939, Patient #1003, ureteral stenosis in conjunction with vesicovaginal fistula 78 days after the index TVM procedure, requiring 2 additional procedures for repair including ureteral reimplantation

[112] ETH-75614, Patient #10026, left ureteral obstruction in conjunction with left ureterovaginal fistula 101 days after the index TVM procedure, requiring 1 additional procedure for repair including ureteral reimplantation; patient subsequently required another procedure for mesh resection, revision of vaginal cuff and TVT

[113] ETH.MESH.03646804: 2 cases of asymptomatic ureteral obstruction after apparently uncomplicated anterior Prolift procedures where intraoperative ureteral patency was demonstrated.

[114] ETH.MESH.00419580. Note the important inaccuracies in this statement. The posterior segment (numbered 3 in the diagram of the total Prolift mesh implant) is NOT positioned in the ischioanal fossa; by way of the cannula-equipped guides, the posterior mesh straps (numbered 6 in the diagram of the total Prolift mesh implant) travel through the ischioanal fossa to exit from skin incisions in the buttock on each side of the patient. The posterior segment of the total Prolift mesh implant is NOT positioned inferior to the levator ani muscle; again, by way of the cannula-equipped guides, the posterior mesh straps travel inferior to the levator ani muscle as they pass through the ischioanal fossa to exit from skin incisions in the buttock on each side of the patient. The posterior segment of the total Prolift mesh implant is positioned in the rectovaginal space, superior to (above) the levator ani muscles laterally and the rectum in the midline.

[115] ETH.MESH.00419581

[116] ETH.MESH.02283250, 02283259

First, Ethicon provided inconsistent instructions as to exactly where the posterior Prolift trocar should be placed through the sacrospinous ligament relative to the ischial spine. In addition, by stating a fixed distance (even if inconsistently) from the ischial spine, Ethicon ignored the fact that the length of the sacrospinous ligament varies from patient to patient, and one fixed distance cannot be correct for all patients. In a study using cadavers from Turkey, the length of the sacrospinous ligament varied from 3.25 cm to 5.46 cm, with a mean of 4.3 cm.[117] In a study using cadavers from the United States, the distance from the ischial spine to the medial border of the sacrum, used as an estimation of the length of the sacrospinous ligament, varied from 4.8 cm to 6.5 cm, with a mean of 5.4 cm.[118] In pelvises with larger obstetric conjugates,[119] the sacrospinous ligament was correspondingly longer. The length of the sacrospinous ligament was shorter in the Turkish study compared with the American study. Different racial characteristics that influence bony anatomy may account for the differences seen in these studies. The results of these studies confirm the clinically important differences in pelvic anatomy between patients and again emphasize how one fixed point cannot be correct in all patients for posterior Prolift trocar placement through the sacrospinous ligament relative to the ischial spine.

Critical neurovascular structures are in close relation to the ischial spine and sacrospinous ligament, including the sciatic nerve, the pudendal complex (vein, artery, and nerve), the levator ani nerve, the pelvic splanchnic nerves,[120] and the inferior gluteal complex (vein, artery, and nerve). In addition, nerves course through the substance of the sacrospinous ligament, with more and larger nerves moving lateral (at the ischial spinous origin) to medial (at the sacral insertion).[121] This area of the pelvis has a rich blood supply; the pudendal and inferior gluteal arteries and veins are of large caliber. Arterial and venous anastomoses are plentiful throughout the pelvis, including anastomoses with the vertebral, internal iliac, and external iliac arteriovenous systems.[122] The clinical importance of such rich anastomotic arteriovenous networks lies in the difficulty of controlling blood loss when an artery and/or vein has been damaged at surgery.[123]

In addition, there is marked variation between patients in the specific branching patterns of the neurovascular structures,[124] which considerably complicates the avoidance of these structures,

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[117] Sagosz N et al. Anatomical landmarks regarding sacrospinous colpopexy operations performed for vaginal vault prolapse. Eur J Obstet Gynecol Reprod Biol 2002; 101: 74-78.

[118] Verdeja A et al. Transvaginal sacrospinous colpopexy: anatomic landmarks to be aware of to minimize complications. Am J Obstet Gynecol 1995; 173: 1468-1469.

[119] The obstetric conjugate is the shortest pelvic diameter through which the fetal head must pass for vaginal birth, measured from the sacral promontory to the top of the pubic symphysis.

[120] Please see Section below for further discussion of damage to the pelvic splanchnic nerves during the posterior or total Prolift procedure and resulting clinical consequences.

[121] Barksdale P et al. Intraligamentous nerves as a potential source of pain after sacrospinous ligament fixation of the vaginal apex. Int Urogynecol J 1997; 8: 121-125.

[122] Barksdale PA et al. An anatomic approach to pelvic hemorrhage during sacrospinous ligament fixation of the vaginal vault. Obstet Gynecol 1998; 91: 715-718.

[123] Barksdale PA et al. An anatomic approach to pelvic hemorrhage during sacrospinous ligament fixation of the vaginal vault. Obstet Gynecol 1998; 91: 715-718.
Thompson JR et al. Anatomy of pelvic arteries adjacent to the sacrospinous ligament: importance of the coccygeal branch of the inferior gluteal artery. Obstet Gynecol 1999; 94: 973-977.

[124] Barksdale PA et al. An anatomic approach to pelvic hemorrhage during sacrospinous ligament fixation of the vaginal vault. Obstet Gynecol 1998; 91: 715-718.

particularly with blind passage of the 2 posterior Prolift trocars. Intraoperative hemorrhage in the area of the sacrospinous ligament occurred in the earliest TVM studies.[125] The Prolift IFUs claimed that attention to patient anatomy would minimize risks.[126] However, this claim is belied by the factors noted above, particularly the marked inter-individual variation in neurovascular branching patterns and the blind passage of the Prolift trocars precluding avoidance of major neurovascular structures. A proper IFU warning would have stated that insufficient knowledge of and/or inattention to patient anatomy would increase the already substantial risks of the blind Prolift trocar passages.

Several aspects of the total or posterior Prolift procedure introduce new and severe intraoperative risks that do not exist with traditional sacrospinous ligament fixation using suture. These include the inferior (underside) approach to the sacrospinous ligament, passage of the posterior Prolift trocar through the ischioanal fossa, the relatively large caliber of the Prolift trocar in relation to the size of the sacrospinous ligament itself and the proximity of critical neurovascular structures, and Prolift mesh implantation that impinges on the rectum. In addition, several aspects of the total or posterior Prolift procedure introduce new and severe postoperative risks that do not exist with traditional sacrospinous ligament fixation using suture. These include the permanent presence of the Prolift mesh implant in close proximity to the critical neurovascular structures and the permanent presence of the Prolift mesh arms in the ischioanal fossa and exiting through the skin of the buttock.

Traditional sacrospinous ligament fixation is performed by attaching sutures under direct visualization to the superior (topside) of the sacrospinous ligament, typically on only one side of the patient (usually the right side, since most surgeons are right-handed). In this way, risk to the nearby critical neurovascular structures is minimized, because most of the critical neurovascular structures pass behind the sacrospinous ligament. In fact, in the era when the superior (topside) approach to traditional sacrospinous ligament fixation was the only technique in use, articles describing the relevant neurovascular anatomy emphasized the importance of avoiding suture placement through the entire thickness of the sacrospinous ligament to minimize the risk of neurovascular injury.[127] However, with the posterior or total Prolift procedure, the posterior Prolift

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Mahakkanukrauh P et al. Anatomical study of the pudendal nerve adjacent to the sacrospinous ligament. Clin Anat 2005; 18: 200-205.

[125] ETH-75617

[126] ETH.MESH.02341527, Original Prolift IFU: "The Gynecare Prolift Pelvic Floor Repair Systems should be used with care to avoid damage to vessels, nerves, bladder and bowel. Attention to patient anatomy and correct use of the device will minimize risks."

ETH.MESH.02341734, Revised Prolift IFU: "Use the Gynecare Prolift Systems with care, and with attention to patient anatomy and to proper dissection technique, to avoid damage to vessels, nerves, bladder, bowel, and vaginal wall perforation. Correct use of the Gynecare Prolift Systems components will minimize risk."

[127] "More importantly, the stitch must be placed as superficial as possible and never across the full thickness of the sacrospinous ligament." Verdeja A et al. Transvaginal sacrospinous colpopexy: anatomic landmarks to be aware of to minimize complications. Am J Obstet Gynecol 1995; 173: 1468-1469.

"Sutures placed through the sacrospinous ligament … without transgressing the entire thickness are in an area generally free of arterial vessels." Thompson JR et al. Anatomy of pelvic arteries adjacent to the sacrospinous ligament: importance of the coccygeal branch of the inferior gluteal artery. Obstet Gynecol 1999; 94: 973-977.

trocar approaches the sacrospinous ligament blindly from the inferior (underside) of the sacrospinous ligament, and the posterior Prolift trocar and subsequently the Prolift mesh arm passes through the full thickness of the sacrospinous ligament. At the very first training session for preceptors, Ethicon received strongly worded feedback about how markedly different this inferior approach and passage through the sacrospinous ligament is for surgeons trained and experienced in traditional vaginal prolapse surgery.[128]

This inferior approach, blind passage, and full-thickness penetration of the sacrospinous ligament in the Prolift procedure greatly and unreasonably increases the risk of injury to critical neurovascular structures that pass posterior to (behind) the sacrospinous ligament. The pudendal complex (vein, artery, and nerve) crosses the ischial spine or very close to the sacrospinous ligament posteriorly and is at risk of injury by the inferior and blind approach to the sacrospinous ligament in the posterior or total Prolift procedure. The levator ani nerve crosses the sacrospinous ligament, and in one study that performed the Prolift procedure on cadavers with subsequent dissection, penetration of the Prolift mesh implant was only 3 mm from the levator ani nerve.[129] To preserve the levator ani nerve, the authors recommended that posterior Prolift trocar penetration of the sacrospinous ligament should be within 5 mm of the lower portion of the sacrospinous ligament. However, this recommendation cannot be reliably followed in the performance of the Prolift procedure, because the lower margin of the sacrospinous ligament may not be visualized by the surgeon, and even if it is, given the blind passage of the posterior Prolift trocar from the inferior approach, the surgeon cannot practicably ensure penetration by the posterior Prolift trocar with precision to one-half of a centimeter (which is approximately the size of the Prolift trocar; see below for further discussion). The inferior gluteal complex (vein, artery, and nerve) passes posterior to the sacrospinous ligament approximately midway between the ischial spine and sacrum, close to the upper border of the lateral half of the sacrospinous ligament, and posterolateral to the pudendal complex.[130] In addition, the coccygeal branch of the inferior gluteal artery passes immediately behind the midportion of the sacrospinous ligament.[131] Again, the inferior and blind approach of the posterior Prolift trocar to and through the sacrospinous ligament greatly increases risk of injury to the inferior gluteal complex, the pudendal complex, and their branches.

"The occurrence of this complication [injury to the perforating cutaneous nerve or posterior femoral cutaneous nerve, causing pain] can be minimized, without reducing the overall success rate of the procedure, by placement of the suture not too deep into the sacrospinous ligament. …" Hefni MA, El-Toukhy TA. Long-term outcome of vaginal sacrospinous colpopexy for marked uterovaginal and vault prolapse. Eur J Obstet Gynecol Reprod Biol 2006; 127: 257-263. Epub 2005 Dec 27.

[128] ETH.MESH.02282833, 10-7-2004, email TVM first training, key learnings: "The TVM represents a MAJOR mind shift on several key aspects of prolapse surgery that may require a greater shift in thinking: … Passage THROUGH the sacrospinal ligaments: -- All of these are new concepts and will require good back up during the education process to explain why they are essential to good results."

[129] Takeyama M et al. Nerve preservation in tension-free vaginal mesh procedures for pelvic organ prolapse: a cadaveric study using fresh and fixed cadavers. Int Urogynecol J 2008 Apr; 19(4): 559-566. Epub 2007 Oct 10.

[130] Sagosz N et al. Anatomical landmarks regarding sacrospinous colpopexy operations performed for vaginal vault prolapse. Eur J Obstet Gynecol Reprod Biol 2002; 101: 74-78.

[131] Thompson JR et al. Anatomy of pelvic arteries adjacent to the sacrospinous ligament: importance of the coccygeal branch of the inferior gluteal artery. Obstet Gynecol 1999; 94: 973-977.

Another aspect of the total or posterior Prolift procedure that introduces new and severe intraoperative risks that do not exist with traditional sacrospinous ligament fixation using suture is passage of the posterior Prolift trocar through the ischioanal fossa. Many of the critical neurovascular structures that pass behind the sacrospinous ligament then travel through the ischioanal fossa, giving off terminal branches to reach their destinations in the pelvis and perineum. The terminal branches of the pudendal nerve passing through the ischioanal fossa are the inferior rectal nerve, perineal nerve, and dorsal nerve of the clitoris. The terminal branches of the pudendal artery are the inferior rectal, perineal, vestibular, and urethral arteries, and the deep and dorsal arteries of the clitoris. The inferior rectal artery is particularly at risk with passage of the posterior Prolift trocars, at a mean distance of only 0.9 cm (range, 0.7-1.1 cm).[132] As noted above, the coccygeal branch of the inferior gluteal artery is at risk of injury from the posterior Prolift trocars passing through the ischioanal fossa. In addition, the rectum is in extremely close proximity to the passage of the posterior Prolift trocars, at a mean distance of only 0.8 cm (range, 0.6-1.0).[133] Some experts believe that true visceral mesh erosion is rare or nonexistent; rather than the mesh eroding into an adjacent organ over some period of time postoperatively, these experts believe that the mesh was inadvertently implanted into an adjacent organ or that visceral injury occurred and was not discovered intraoperatively.[134] It is well known that visceral injury is much less morbid and more easily treated when it is discovered and managed intraoperatively; conversely, if visceral injury, particularly related to mesh implantation, is not recognized intraoperatively and is only recognized postoperatively when the patient develops a complication, then the visceral injury is much more difficult to treat successfully, mesh explantation is almost always necessary, and the patient incurs much more morbidity. Given that situation, if Ethicon had patient safety as its highest priority, Ethicon would have done everything it could to fully warn surgeons of the risks of Prolift trocar-related and mesh-related visceral injury and to inform them about how best to diagnose and manage intraoperative injury with the Prolift procedure. However, Ethicon did not do that. Neither the original Prolift IFU nor the Prolift surgical technique document even mentioned rectal examination to detect rectal injury. Even when the Prolift IFU was revised to include rectal examination, Ethicon failed to inform surgeons of the critically important issue of the timing of rectal examination to detect rectal injury BEFORE Prolift mesh implantation had taken place. Ethicon has never revised the Prolift surgical technique document to address these issues.

Another aspect of the total or posterior Prolift procedure that introduces new and severe intraoperative risks that do not exist with traditional sacrospinous ligament fixation using suture is the relatively large caliber of the Prolift trocar in relation to the size of the sacrospinous ligament itself and the proximity of critical neurovascular structures. The Prolift cannula-equipped guide (trocar) has a diameter of 4.5 mm.[135] The pudendal complex, comprising the pudendal vein, artery,

[132] ETH-02601: Chen CCG et al. Anatomic relationships of the tension-free vaginal mesh trocars. Am J Obstet Gynecol 2007; 197: 666.e1-666.e6.
[133] ETH-02601: Chen CCG et al. Anatomic relationships of the tension-free vaginal mesh trocars. Am J Obstet Gynecol 2007; 197: 666.e1-666.e6.
[134] Roundtable: Using mesh to repair prolapse: Averting, managing complications. Karram MM, moderator. OBG Management 2009; 21 (2): 21-28. Dr. Raz: "… unrecognized bladder, urethral, and vaginal perforation are the most common reasons for the complications." Dr. Walters: "I do not believe that mesh 'erodes' into the bladder, urethra, or rectum, but that it is placed there inadvertently and overlooked intraoperatively. …"
[135] ETH-03284: Cannula tubing shall have an OD [outer diameter] of 4.50 + 0.20 mm/-0.10 mm.

and nerve, is rather broad, measuring between 7 mm and 8 mm,[136] while the distance between the ischial spine and the pudendal complex ranges from 0 mm to 5.5 mm.[137] Therefore, to avoid injury to these nearby neurovascular structures, the surgeon must pass the 4.5-mm trocar, blindly and from the inferior approach, sufficiently far from the ischial spine to avoid injury to the pudendal complex, while at the same time, avoiding the coccygeal branch of the inferior gluteal complex that passes behind the midportion of the sacrospinous ligament, and avoiding the inferior gluteal complex itself as it passes close to the upper border of the lateral half of the sacrospinous ligament.

Another aspect of the total or posterior Prolift procedure that introduces new and severe intraoperative risks that do not exist with traditional sacrospinous ligament fixation using suture is Prolift mesh implantation that impinges on the rectum. The posterior Prolift mesh body is implanted over the rectum, and the 2 posterior Prolift mesh arms on each side anchor the posterior Prolift mesh body by passing through the sacrospinous ligaments. Although the Prolift surgical technique document states that "optimally, the posterior segment of the total [Prolift] implant will be positioned tension-free above the rectum,"[138] Ethicon has acknowledged in deposition testimony that no objective criteria or mechanism exists to ensure "tension-free" Prolift mesh implantation.[139]Posterior Prolift mesh implanted under tension can cause pore collapse, banding, contraction, pain, symptoms of obstructed defecation, and Prolift mesh erosion into the vagina and rectum.

The total or posterior Prolift procedure also introduces new and severe postoperative risks that do not exist with traditional sacrospinous ligament fixation using suture, including the permanent presence of the Prolift mesh implant in close proximity to critical neurovascular structures and the permanent presence of the Prolift mesh arms in the ischioanal fossa and exiting through the skin of the buttock. With traditional sacrospinous ligament fixation, one or more sutures are attached to the sacrospinous ligament and then attached to the apex of the vagina to provide apical support. The type of suture used may be absorbable, delayed absorbable, or permanent. If absorbable sutures of any type are used, infringement or entrapment of pelvic nerves will only be temporary as the sutures eventually dissolve. For this reason, pain suspicious of neuropathic origin after traditional sacrospinous ligament fixation will often be managed conservatively, with the expectation that the pain will resolve as the sutures dissolve. However, if permanent suture has been used and neuropathic pain occurs postoperatively, it is commonly necessary to remove the suture. Fortunately, this is a relatively simple procedure, and once the suture is located and cut, it slides through the tissue easily for removal with no further tissue damage. In the only published case report that could be found, 2 years after the index surgery, symptom resolution after suture removal was immediate, complete, and long-lasting.[140]

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[136] Verdeja A et al. Transvaginal sacrospinous colpopexy: anatomic landmarks to be aware of to minimize complications. Am J Obstet Gynecol 1995; 173: 1468-1469.
[137] Sagosz N et al. Anatomical landmarks regarding sacrospinous colpopexy operations performed for vaginal vault prolapse. Eur J Obstet Gynecol Reprod Biol 2002; 101: 74-78.
[138] ETH.MESH.00419585
[139] David Robinson dep., 184:13-189:8
[140] Alevizon SJ, Finan MA. Sacrospinous colpopexy: management of postoperative pudendal nerve entrapment. Obstet Gynecol 1996; 88 (4 Pt 2): 713-715.

In contrast, the total or posterior Prolift procedure results in the permanent presence of the Prolift mesh implant in close proximity to critical neurovascular structures and adjacent pelvic organs. Even if direct damage was avoided at the time of posterior Prolift trocar placement, the chronic and sometimes severe inflammatory and foreign body reaction to the Prolift mesh implant can result in subsequent damage.[141] Scarring and marked fibrosis can envelop nearby structures, causing clinical conditions such as delayed pudendal nerve entrapment. When this occurs, in stark contrast to the relative ease of permanent suture removal, complete permanent Prolift mesh removal is difficult if not impossible to perform, and the risk of creating significant new morbidity is very high. Testifying before the FDA Advisory Panel on transvaginal mesh surgery in September 2011, one surgeon experienced in permanent mesh removal described it in this way:

> "What it's like to remove mesh from the surgeon's perspective can perhaps be appreciated by this analogy. Extirpation of vaginal mesh is akin to taking a hammer and chisel and trying to remove the rebar from a sidewalk while leaving the cement otherwise intact and not damaging the water mains and power lines below. It is difficult if not impossible to remove all the mesh and do it safely."[142]

In addition, symptom resolution is by no means assured, even if somehow the surgeon manages to remove all of the Prolift mesh. By that point, the chronic inflammatory reaction may have become so established as to be "self-perpetuating," in that the previous and current tissue damage caused by Prolift mesh implantation may be so extensive, with the release of so many cellular products associated with cell death, inflammation, and tissue damage, that the inflammatory and fibrotic cycle cannot be broken. This accounts, in part, for the phenomenon described by the FDA in its second public health communication regarding transvaginal mesh in prolapse surgery, that stated "Removal of mesh due to mesh complications may involve multiple surgeries and significantly impair the patient's quality of life. Complete removal of mesh may not be possible and may not result in complete resolution of complications, including pain."[143]

Another aspect of the total or posterior Prolift procedure that introduces new and severe postoperative risks that do not exist with traditional sacrospinous ligament fixation using suture is the permanent presence of the Prolift mesh arms in the ischioanal fossa and exiting through the skin of the buttock. As noted above, major neurovascular structures pass behind the ischial spine and sacrospinous ligament to enter and cross the ischioanal fossa on their way to their terminal destinations in the pelvis. The permanent presence of the Prolift mesh arms incites a chronic inflammatory and foreign body reaction that may affect these neurovascular structures, as well as the rectum. As the bilateral posterior Prolift mesh arms retract as they pass near the rectum on each side, along with retraction affecting the body of the posterior Prolift mesh itself, this retraction can tighten the Prolift mesh body over the surface of the rectum, resulting in symptoms of obstructed defecation and Prolift mesh erosion into the rectum.

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[141] June 2, 2006, Ethicon Expert Meeting, Meshes for Pelvic Floor Repair, ETH-80646, Biological response to surgical mesh, Professor Klosterhalfen: "Meshes can cause Nerve damage due to mechanical irritation (mesh bears on nerve)"
[142] http://commonhealth.wbur.org/2011/11/surgery-under-scrutiny-what-went-wrong-with-vaginal-mesh, 11-4-2011
[143] FDA Safety Communication: UPDATE on serious complications associated with transvaginal placement of surgical mesh for pelvic organ prolapse, July 13, 2011

Vaginal dissection

Surgeons experienced with traditional vaginal prolapse surgery (anterior and posterior colporrhaphy) will not typically be experienced in performing dissection of the entire thickness of the anterior or posterior vaginal wall. Rather, most will have been trained in anterior and posterior colporrhaphy, where the vaginal wall is split, lifting the epithelial layer and leaving most of the muscularis layer covering the bladder and rectum, respectively.[144] Dr. Kevin Benson, who implanted Linda Gross's Prolift, testified that he had been using a split thickness dissection prior to the Prolift, and at the time he operated on Linda Gross the hydrodissection technique "was just in its infancy."[145] Ethicon was well aware that the full-thickness vaginal dissection in the Prolift procedure is "counterintuitive" to surgeons and requires that they be trained to perform this dissection differently from what they learned during their surgical training.[146] For example, Scott Jones confirmed this in his deposition testimony.[147].

The Prolift IFU provides no information about vaginal dissection and the importance of performing the vaginal dissection in the correct plane. In the Prolift surgical technique document, surgeons are instructed to enter the vesicovaginal space (the potential space between the vagina and bladder)[148] anteriorly and the rectovaginal space (the potential space between the vagina and rectum)[149] posteriorly. However, the Prolift surgical technique document provides no information on exactly how to ensure that vaginal dissection is performed in the correct plane, how to determine that the correct space has been entered, and how to protect the bladder, ureters, and rectum from injury during vaginal dissection. Again, these issues illustrate the unnecessary complexity and risk level introduced by the Prolift.

Even the surgical videos produced by Ethicon as training aids provide inaccurate or incomplete information as to the specific technique of full-thickness vaginal incision and dissection necessary for the Prolift procedures. The video that provides a stylized depiction of procedural

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[144] ETH-02707-02708, Expert opinion from experienced Prolift surgeons, under the heading of Anesthesia and Hydrodissection: "Historical teaching in vaginal surgery effectively emphasized splitting the fibromuscular coat of the vaginal epithelium to allow the creation of a plication layer. Even today, most surgeons employ a very thin dissection of the vaginal wall, …."

[145] Benson dep., 77:9-80:2

[146] ETH-74425, 2-7-2007, panel discussion of mesh prolapse repair, moderated by Dr. Kirkemo: "… First, the plane of dissection in the vaginal wall needs to be in a deeper plane than we are accustomed to …"
ETH-02707-02708, Heading Anesthesia and Hydrodissection: "Historical teaching in vaginal surgery effectively emphasized splitting the fibromuscular coat of the vaginal epithelium to allow the creation of a plication layer. Even today, most surgeons employ a very thin dissection of the vaginal wall, which devascularizes the epithelium and provides no positive impact in this technique. … Learning this technique in the operating room with surgeons experienced in accessing these spaces vaginally may be critical …"

[147] Scott Jones dep., 838:21-839:21

[148] "Perform a dissection of the entire thickness of the anterior vaginal wall. It is preferred to leave Halban's fascia (pubocervical fascia) on the vaginal wall." (Prolift surgical technique document, Anterior Dissection, page 5; ETH.MESH.00419575)

[149] "Care should be taken when separating the rectum from the entire thickness of the vagina. Dissection of the entire thickness of the posterior vaginal wall should be performed starting from the vaginal incision and continued up to the apex of the vagina." (Posterior Dissection, page 9; ETH.MESH.00419579)

steps for anterior and posterior Prolift procedures depicts the vesicovaginal and rectovaginal spaces as large spaces between the vagina and bladder and the vagina and rectum, respectively, rather than depicting these spaces accurately as potential spaces only.[150] For surgeons inexperienced in full-thickness vaginal incision and dissection, these inaccurate depictions provide misleading information as to the true proximity of the vagina and its adjacent organs, the bladder and rectum. Two surgical videos incorrectly describe the vaginal layers that should be incised to reach the vesicovaginal or rectovaginal space.[151] None of the videos describe or depict how to ensure that the vaginal incision is full thickness or that vaginal dissection is being performed in the correct space.[152] None of the videos adequately describe or depict how to minimize the risk of bladder, ureteral, and rectal injury during the described vaginal incision and dissection.[153]

Because the space between the vagina and bladder or rectum is exceedingly thin, entrance into the correct space is less likely and injury to the bladder or rectum is more likely in the Prolift procedures, compared with traditional vaginal prolapse surgery. This is verified by the higher frequency of bladder and rectal perforation during Prolift procedures, compared with traditional vaginal prolapse surgery.[154] This also results in higher risk of significant bleeding.[155]

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[150] ETH.MESH.PM.000001: stylized depiction of Prolift procedural steps in the Anterior Repair segment and the Posterior Repair segment

[151] ETH.MESH.PM.000001 Posterior Repair segment: "The rectovaginal space is easily developed surgically by incising the lower half of the posterior epithelium, full thickness, and opening the space with the finger."
ETH.MESH.PM.000032 total Prolift with uterine conservation: "A full thickness incision extending from the vaginal epithelium to the fibroconnective layer is done."

[152] ETH.MESH.000001: stylized depiction of Prolift procedural steps in the Anterior Repair segment and the Posterior Repair segment; surgical videos depicting a total Prolift procedure with uterine conservation and a total Prolift procedure with vaginal hysterectomy; ETH.MESH.000058: surgical video depicting total Prolift procedure for posthysterectomy prolapse; ETH.MESH.000057: surgical video depicting anterior Prolift procedure with laparoscopic visualization; ETH.MESH.000032: surgical videos depicting an anterior Prolift procedure, a posterior Prolift procedure, a total Prolift procedure with uterine conservation, and a total Prolift procedure for posthysterectomy prolapse.

[153] ETH.MESH.000001: stylized depiction of Prolift procedural steps in the Anterior Repair segment and the Posterior Repair segment; surgical videos depicting a total Prolift procedure with uterine conservation and a total Prolift procedure with vaginal hysterectomy; ETH.MESH.000058: surgical video depicting total Prolift procedure for posthysterectomy prolapse; ETH.MESH.000057: surgical video depicting anterior Prolift procedure with laparoscopic visualization; ETH.MESH.000032: surgical videos depicting an anterior Prolift procedure, a posterior Prolift procedure, a total Prolift procedure with uterine conservation, and a total Prolift procedure for posthysterectomy prolapse.

[154] PLTMEDLIT00139, Diwadkar GB, Barber MD, Feiner B, Maher C, Jelovsek JE. Complication and reoperation rates after apical vaginal prolapse surgical repair: a systematic review. Obstet Gynecol 2009 Feb; 113: 367-373. Cystotomy in traditional vaginal prolapse surgery, 0.4% (95% CI 0.2-0.5); cystotomy with mesh kits, 0.7% (95% CI 0.4-1.0).
Altman D, Vayrynen T, Engh ME et al (2011) Anterior colporrhaphy versus transvaginal mesh for pelvic-organ prolapse. N Engl J Med 364(19):1826–1836. Bladder perforation in 1 patient (0.5%) with anterior colporrhaphy, versus 7 patients (3.5%) with anterior Prolift.

[155] Altman D, Vayrynen T, Engh ME et al (2011) Anterior colporrhaphy versus transvaginal mesh for pelvic-organ prolapse. N Engl J Med 364(19):1826–1836. Hemorrhage > 500 mL, no patients with anterior colporrhaphy versus 5 patients (2.5%) with anterior Prolift.

Dissection to expose the sacrospinous ligament on both sides

The Prolift surgical technique document describes posterior vaginal and pelvic dissection, in preparation for the placement of the posterior segment of the Prolift mesh implant.[156] In contrast to dissection required for a traditional sacrospinous ligament fixation procedure, more extensive and bilateral dissection must be carried out for the Prolift procedure, unreasonably increasing the risk of injury.[157,158]

Bladder Plication

The appropriate surgical technique for managing anterior vaginal prolapse is to recreate support for the anterior vagina; nothing need be or should be done to the bladder itself. Despite this, Ethicon recommends placing sutures (plication) in the bladder wall in order to address deficiencies in the performance of the mesh implant.[159] The portion of the bladder affected includes the trigone and ureteral orifices. Bladder plication is an unnecessary and dangerous step that unreasonably increases the immediate risk of intraoperative bladder and ureteral injury.

In addition, reaction to suture in the bladder wall in combination with the overlying mesh increases the risk of postoperative mesh erosion into the bladder and the risk of postoperative vesicovaginal fistula, ureterovaginal fistula, and ureteral obstruction. Furthermore, damage to tissue in the trigone of the bladder, reaction to suture in the bladder wall, and the reduced bladder capacity caused by bladder plication, in combination with the overlying mesh, increases the risk of postoperative urinary dysfunction such as urinary urgency, frequency, and urge incontinence.

Rectal plication

The appropriate surgical technique for managing posterior vaginal prolapse is to recreate support for the posterior vagina; nothing need be or should be done to the rectum itself. Despite this, in order to address deficiencies in the performance of the mesh implant, Ethicon recommends placing sutures (plication) in the prerectal fascia.[160] This instruction is confusing and dangerous, as there is no "prerectal fascia"; sutures placed from the rectovaginal space are placed directly into the

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[156] Prolift surgical technique document: "Dissection of the entire thickness of the posterior vaginal wall should be performed starting from the vaginal incision and continued up to the apex of the vagina. Laterally, the dissection opens the pararectal spaces and follows the space between the rectum and the levator ani muscle until the sacrospinous ligament can be palpated [on the right and left side of the patient]. … Further deep dissection should then be performed to expose both sides of the sacrospinous ligament at the level of the ischial spine [on the right and left side of the patient]." (page 9, ETH.MESH.00419579)

[157] ETH.MESH.02282833, 10-7-2004, email TVM first training, key learnings: "The dissection of the posterior compartment for this procedure is significantly different to that for either standard sacro-spinous fixation procedures (Richter) or for even posterior IVS. The main difference is the degree of lateral dissection to the [sic] create the space for the mesh out to the Arcus Tendinous. It was considered more technically challenging that they had thought."

[158] 12-1-2005, ETH-80640, Notes from Prolift roundtable discussion with experienced Prolift surgeons: "Ensure dissection is complete. That is, the sacrospinous ligament is completely cleared of tissue otherwise it will become entangled in the RD [retrieval device]. More dissection is required than a regular SSLF [sacrospinous ligament fixation]."

[159] "At this point, if required, plication of the bladder is performed in order to reduce the cystocele." (Prolift surgical technique document, top, page 6; ETH.MESH.00419576)

[160] "At this point, if required, a plication of the prerectal fascia in order to reduce the rectocele should be performed." (Prolift surgical technique document, page 9; ETH.MESH.00419579)

muscular layer of the rectum. This is clearly depicted in one of the surgical videos, in which the narrating surgeon describes and depicts that "Here are the vertical longitudinal fibers of the anterior rectal wall" during dissection in the rectovaginal space after full-thickness posterior vaginal incision.[161]

Rectal plication is an unnecessary and dangerous step that unreasonably increases the immediate risk of intraoperative rectal injury. In addition, reaction to suture in the rectal wall in combination with the overlying mesh increases the risk of postoperative complications such as mesh erosion into the rectum and rectovaginal fistula. Furthermore, reaction to suture in the rectum and the reduced rectal capacity caused by rectal plication increases the risk of postoperative defecatory dysfunction such as urgency, frequency, and fecal incontinence.

Feedback from experienced Prolift surgeons to avoid bladder and rectal plication

Ethicon convened forums to obtain feedback from experienced Prolift surgeons. The feedback from these surgeons was that bladder and rectal plication should not be performed under the Prolift mesh implant.[162] Despite this, Ethicon did not revise the Prolift surgical technique document.

Inadequate guidance from Ethicon about how to perform the Prolift procedure in the safest and most effective manner

Risks of Uterine Conservation

The protocol for the French TVM study required concomitant hysterectomy if women had not already had previous hysterectomy.[163] Early retrospective results from the French TVM group suggested that concomitant hysterectomy increased the frequency of vaginal mesh exposure, and strong recommendations were made to practice uterine conservation when performing the TVM or Prolift procedures.[164] However, some later reports refuted that concomitant hysterectomy was the key factor responsible for an increased risk of vaginal mesh exposure. One study reported a low frequency of vaginal mesh exposure (2.5%, 1 in 40 patients) with specific Prolift technique modifications, including separate incisions for hysterectomy versus Prolift mesh placement and not passing the midportion of the total Prolift implant behind the vaginal cuff.[165]

Nevertheless, uterine conservation with the Prolift procedure gained popularity, at least in part because Ethicon marketed the Prolift procedure to patients specifically as a procedure that

[161] ETH.MESH.000032: surgical video depicting posterior Prolift procedure, video time 2:25 to 2:30.
[162] Prolift Forums and Round Table Summary, 12-3-2005, 12-1-2005, 11-16-2005, under the heading of Additional Repairs: "No repairs under the mesh." (ETH-19945)
Expert opinion on the Prolift Systems, under the heading of Additional Sutures: "It is strongly recommended that no plication stitches be used under the mesh." (ETH-02709)
[163] ETH.MESH.02813043
[164] ETH-02794: Collinet P et al. Transvaginal mesh technique for pelvic organ prolapse repair: mesh exposure management and risk factors. Int Urogynecol J 2006 Jun; 17(4): 315-320. Epub 2005 Oct 15.
[165] Murphy M et al. Vaginal hysterectomy at the time of transvaginal mesh placement. Female Pelvic Med Reconstr Surg 2010; 16: 272-277.

could be performed without the need for hysterectomy.[166] Despite Ethicon's implied assertion that uterine conservation was a new and unique feature of the Prolift procedure, uterine conservation with a variety of traditional prolapse procedures has been well reported in the medical literature, including sacrohysteropexy (or sacrocervicopexy), sacrospinous ligament fixation, and uterosacral ligament suspension.[167,168,169,170,171,172,173,174]

Subsequent studies reported that uterine conservation with the Prolift procedure resulted in untoward effects, including more frequent mesh retraction and more frequent recurrent prolapse. An early abstract from the French TVM group reported recurrent prolapse (defined as ≥ POPQ stage II) more frequently in women after the Prolift procedure with uterine conservation (13 of 164, 8%) compared with none in 53 women who had previous hysterectomy at only 10 weeks of follow-up.[175] The frequency of vaginal mesh exposure did not differ, but mesh contraction occurred more frequently in women with uterine conservation (20%) and previous hysterectomy (21%), versus concomitant hysterectomy (9%).

In a large cohort study of 433 women undergoing the Prolift procedure, combined anterior and posterior Prolift mesh implantation with uterine conservation was independently associated with all definitions of failure (defined as anatomic outcome ≥ stage II in the mesh-treated compartment; ≥ stage II in all compartments; and a composite outcome of overall prolapse beyond the hymen, bulge symptoms, or reoperation for recurrent prolapse).[176] The adjusted odds ratio (with 95% confidence interval [CI]) for failure in the mesh-treated compartment was 2.65 (1.21-5.81); for failure in all compartments, 5.40 (2.38-12.21); and for failure defined as the composite outcome, 7.81 (1.62-37.60). Since the risk of failure was so greatly increased with combined anterior and posterior Prolift mesh implantation with uterine conservation, the authors suggested alternative modes of treatment, including anterior mesh implantation with sacrospinous

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[166] ETH.MESH.00000012, Prolift patient advertising, Heading "Gynecare Prolift is different from other surgical alternatives": "The [Prolift] procedure … may avoid the need for hysterectomy as long as the uterus is not diseased." ETH.MESH.00016663, Prolift patient brochure, Heading "What is Gynecare Prolift?": "Using this new surgical procedure there is often no need to perform hysterectomy if the uterus itself is not diseased."

[167] Maher CF et al. Laparoscopic suture hysteropexy for uterine prolapse. Obstet Gynecol 2001; 97: 1010-1014.

[168] Krause HG et al. Laparoscopic sacral suture hysteropexy for uterine prolapse. Int Urogynecol J 2006; 17: 378-381. Epub 2005 Nov 30.

[169] Van Brummen HG et al. Sacrospinous hysteropexy compared to vaginal hysterectomy as primary surgical treatment for a descensus uteri: effects on urinary symptoms. Int Urogynecol J 2003; 14: 350-355.

[170] Diwan A et al. Uterine preservation during surgery for uterovaginal prolapse: a review. Int Urogynecol J 2004; 15: 286-292. 14 articles reviewed.

[171] Maher CF et al. Uterine preservation or hysterectomy at sacrospinous colpopexy for uterovaginal prolapse? Int Urogynecol J 2001; 12: 381-385.

[172] Barranger E et al. Abdominal sacrohysteropexy in young women with uterovaginal prolapse: long-term follow-up. Am J Obstet Gynecol 2003 Nov; 189: 1245-1250.

[173] Ridgeway B et al. Hysteropexy. A review. Minerva Ginecol 2008 Dec; 60: 509-528.

[174] Price N et al. Laparoscopic hysteropexy: the initial results of a uterine suspension procedure for uterovaginal prolapse. BJOG 2010 Jan; 117: 62-68.

[175] ETH-03220: (abstract #89) Cosson M et al. Preservation of uterus when treating prolapse by Prolift does not significantly reduce risk of early post surgical complications and failures.

[176] Milani AL, Withagen MI, Vierhout ME. Outcomes and predictors of failure of trocar-guided vaginal mesh surgery for pelvic organ prolapse. Am J Obstet Gynecol 2012; 206: 440.e1-8. Epub 2012 Feb 1.

hysteropexy and posterior colporrhaphy if needed, or supracervical laparoscopic sacrocolpopexy, clearly indicating that the total Prolift procedure with uterine conservation is not adequate for durable treatment of uterovaginal prolapse. This finding flatly contradicts Ethicon's implied assertion in its advertising to patients that uterine conservation has no effect on the outcome of the Prolift procedure. It is particularly egregious that Ethicon aggressively marketed the Prolift procedure to patients by stressing that uterine conservation was possible, while at the same time promising a long-lasting solution for prolapse,[177] when in fact, Ethicon was setting women up for failure of the Prolift procedure at a rate almost 8 times higher than if hysterectomy had been performed.

In addition to a higher frequency of mesh-related complications and failure of the Prolift procedure with uterine conservation, other important complications can occur related to the uterus itself. Among 369 women with uterine conservation in a large series of the Prolift procedure, 2 patients later developed postmenopausal bleeding, managed with laparoscopic total hysterectomy; pathology findings were benign.[178] Less common but vastly more serious is the development of cancer. In that same series, 1 woman died of endometrial cancer 3 years after the Prolift procedure with uterine conservation, despite preoperative ultrasound that showed no endometrial thickening.[179] In a series of 644 patients who underwent hysterectomy at the time of prolapse surgery, unexpected pathology was found in 17 patients (2.6%), including premalignant changes in 15 patients and endometrial cancer in 2 patients.[180] The authors recommended that "…in women with a history of postmenopausal bleeding, even with a negative endometrial evaluation, we do not recommend uterine preservation at the time of prolapse surgery." Unfortunately, the most lethal form of endometrial cancer may not show endometrial thickening by ultrasound.[181] Since the lifetime risk of uterine and cervical cancer is 3.3% (1 in 30 women),[182] patients should be counseled accordingly when considering uterine conservation with the Prolift procedure. Also, the potential difficulties in treatment of such cancers due to the presence of the permanent Prolift mesh should have been addressed. Ethicon never addressed this in any of its marketing of the Prolift procedure to physicians and patients.

VI. The Prolift procedures are Routinely Performed with Variations from the "Standardized" Technique

[177] ETH-00264, Prolift advertising directed to patients: "Now a new and revolutionary surgical procedure offers promising long-term results and a long-lasting solution for women with pelvic organ prolapse."
[178] De Landsheere L et al. De Landsheere L, Ismail S, Lucot J-P, Deken V, Foidart J-M, Cosson M. Surgical intervention after transvaginal Prolift mesh repair: retrospective single-center study including 524 patients with 3 years' median follow-up. Am J Obstet Gynecol 2012; 206: 83.e1-7.
[179] De Landsheere L et al. De Landsheere L, Ismail S, Lucot J-P, Deken V, Foidart J-M, Cosson M. Surgical intervention after transvaginal Prolift mesh repair: retrospective single-center study including 524 patients with 3 years' median follow-up. Am J Obstet Gynecol 2012; 206: 83.e1-7.
[180] Frick AC et al. Risk of unanticipated abnormal gynecologic pathology at the time of hysterectomy for uterovaginal prolapse. Am J Obstet Gynecol 2010 May; 202: 507.e1-4.
[181] Dimatraki M et al. Clinical evaluation of women with PMB: Is it always necessary an endometrial biopsy to be performed? A review of the literature. Arch Gynecol Obstet 2011; 283: 261-266.
[182] http://www.cancer.org/Cancer/CancerBasics/lifetime-probability-of-developing-or-dying-from-cancer

Various Ethicon employees have suggested in their testimony that Prolift complications can be due to physicians' variations from the "standard" Prolift procedure. For example, Aaron Kirkemo asserted: "in my experience, the exposures that I've seen have been due to technical issues."[183] Although it is undoubtedly true that some complications occur due to the implantation technique and surgical steps taken during implantation of a Prolift, it is not reasonable for Ethicon to attempt to shift blame to physicians on this basis. In fact, Aaron Kirkemo later admitted that exposures can occur when the surgeon is skilled, and "not because the doctor did anything wrong, but just because it's one of the risks…exposures will occur. I mean, nobody has a zero exposure rate."[184]

The first sentence of the Prolift surgical technique document states that "The objective of the Prolift procedure is to achieve a complete anatomic repair of pelvic floor defects in a standardized way."[185] However, although Ethicon offers a technique with default surgical steps to implant the Prolift Systems, in reality, the procedures performed on individual patients must of necessity vary in material ways based on factors such as patient anatomy, patient medical conditions, surgical and medical judgment, and physician skill level and training variations. Moreover, the central technique of the Prolift procedures, "tension-free" placement of the mesh implant, has not been standardized on any objective basis, and other important aspects of the Prolift procedure regarding placement of the mesh implant have not been truly standardized.

It is critical to recognize and understand that surgery for the treatment of pelvic organ prolapse is by necessity varied from patient to patient, based in large part on the surgeon's judgment and experience. David Robinson testified that the Prolift design took into account factors such as varying patient presentations, and varying physician skill levels, decision making, and judgment. "So we are well aware physicians modify the use…to fit the occasion." David Robinson testified at length regarding the fundamental role of medical judgment.[186] Paul Parisi also testified at length to Ethicon's knowledge of the many variations to the Prolift procedure depending on patient differences, physician differences, and medical and surgical judgment, for example.[187] The patent filed for the TVM/Prolift procedure actually claims ownership of the foreseeable "variations and modifications" to the Prolift procedure.[188]

As set forth above, Ethicon has acknowledged that it was well-known that surgeons utilizing the Prolift would modify and alter, and vary the procedure based upon multiple factors including their judgment, patient anatomy, patient medical conditions, and training. Any and all of these variations and modifications to the procedure would come within "the spirit and scope" of the Prolift procedure.

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[183] Aaron Kirkemo dep., 153:19-23
[184] Aaron Kirkemo dep., 159:19-160:3
[185] Prolift surgical technique document, first sentence under the heading of Principles of the Procedure (page 2, ETH.MESH.00419572)
[186] David Robinson dep., 131:24-132:9; 182:3-184:12; 193:10-16; 199:1-15; 200:15-20; 209:14-20; 260:25-261:3.
[187] Paul Parisi dep., 421:2-425:2; 507:6-508:11; 546:25-547:14; 559:18-25; 592:16-22; 598:12-19.
[188] ETH-07434-07494

The attempt by Ethicon to standardize the steps of the procedure, down to providing specific locations of and distances between key anatomic landmarks, is a convention of commercialization, divorced from the core training of physicians and the practice of pelvic floor surgery.

For example, the Prolift surgical technique document directs that the posterior trocars be placed "approximately 3-4 cm medial to the ischial spine…,"[189] yet the distance from the ischial spine to the sacrospinous ligament will vary from patient to patient, due to factors such as variations in pelvic anatomy related to race, height, age, and associated medical conditions. Thus, a prescribed distance must be wrong for many patients. In fact, there was controversy during the preparation of the animated procedural video for the Prolift procedure, regarding the correct placement of the posterior trocars in relation to the distance from the ischial spine along the sacrospinous ligament, with the French TVM group insisting the distance should be "2 cm" and consulting anatomist Robert Rogers, M.D. insisting the distance should be 3-4 cm.[190] In June 2005,

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[189] Prolift surgical technique document, under the heading of "Preparation for Placement of the Posterior Segment: "The Cannula-Equipped Guide is advanced until it is contact with the inferior side of the sacrospinous ligament approximately 3-4 cm medial to the ischial spine. …" (page 11, ETH.MESH.00419581)

[190] ETH.MESH.00028840, Email chain about passage of posterior trocars through sacrospinous ligament relative to ischial spine:
From Kendra Munchel to Ophelie Berthier, 6-2-2005
"I received your voicemail about changing the animation and script per the posterior repair. To change the verbiage from 3-4 cm to 2 cm is another major change. The scripts would have to be re-recorded, digitized, as well as changing the animation. This would cost us more money and time.
I spoke with R. Rogers, MD and he believes this distance from the ischial spine is accurate and provides a 'safe' zone for passage of the instruments.
Additionally, I am certain this measurement is in the surgical technique document. This would need to be changed too. Please let me know if you have more money and more time. I can tell you that I am struggling to pay all the bills with the original PO [purchase order]."
From Ophelie Berthier to Kendra Munchel and others, 6-2-2005
"We had this discussion with the TVM group yesterday and they said that if you cross at 3-4 cm from the ischial spine on the sacrospinous ligament, then you reach the sacrum which is not right. It is at 2 cm in the medial part of the sacrospinous ligament.
The group said we must do this change. If we cannot redo the voiceover which I understand, could we at least change it on the written script of the CD+ on the 3D images. We can at least change the voiceover for the other versions.
Scott was also planning on asking Charlotte to validate the change on the procedure description document. Can you ask Jeff, what would [b]e the additional cost for just changing the 3D (which is replace 3-4cm by 2cm) and just the text which will be written in front as well as integrating this change in the procedure description document.
This is too key to be left out. …"
From Jeff Levy (Reflective Learning) to Kendra Munchel and others, 6-2-2005
"We can make these changes for you today. …
We will take out the 3-4 cm and replace it with 2 cm. Is that correct? …"
From Allison London Brown to Jeff Levy and others, 6-2-2005
"Yes that is correct. Jeff how will this impact our timeline"
From Ophelie Berthier to Jeff Levy and others, 6-2-2005
"Yes that is correct. Thanks a lot."
ETH.MESH.00029162, Email chain about passage of posterior trocars through sacrospinous ligament in relation to ischial spine:
From Kendra Munchel to Charlotte Owens, 6-3-2005
"I received another message from R. Rogers, MD who stands by the distance of 3-4 cm medial from the ischial spine for the posterior passage. He has performed many cadaver dissections whereby he has come to this conclusion.

Ethicon determined as a compromise that the distance should be described as "approximately 2 cm," but the Prolift surgical technique document was not revised to be consistent.[191] It is particularly concerning that this controversy was going on in June 2005, more than 2 months after launch of the Prolift Systems. This has at least 2 important implications: 1) well after Prolift launch, Ethicon had not yet determined the optimal placement of the posterior Prolift trocar passage through the sacrospinous ligament relative to the ischial spine, surely a key point that should have been determined during the development of the Prolift procedure; and 2) professional educational tools had not been completed prior to Prolift launch to provide essential surgical teaching to surgeons on the new and unique procedures that the Prolift Systems represented.

Aside from the troubling and dangerous lack of consistency between two important physician training resources, and the fact that Ethicon failed to resolve this issue in a consistent manner, the bottom line is that the search for an exact distance for this key step for inserting the posterior Prolift trocars of this pre-packaged kit is contrary to how surgery is actually practiced in adapting to the needs of individual patients. This introduces further risk.

Adding to the confusion and inconsistency, the surgical videos produced by Ethicon as training aids provided contradictory information as to the correct placement of the posterior Prolift trocars in relation to the distance from the ischial spine along the sacrospinous ligament. In certain cases, inconsistency exists even within the same video. In the video depicting a stylized version of the Prolift procedural steps, narration describes passage of the posterior cannula-equipped guide

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I share this information with you as I have not performed the measurements myself. Additionally, I do not want to be held accountable for this measurement.

Please note that we are making the measurement changes to the CDROM based on feedback from the French team. For the record, I think we should recommend for the device to be passed in the mid-portion of the sacrospinous ligament versus giving a precise measurement. …"

From Charlotte Owens to Kendra Munchel, 6-3-2005

"You make an excellent point and I would send an email to me and Scott with that suggestion so that we do not make an error. It is a good mid point to satisfy all."

From Kendra Munchel to Charlotte Owens and others, 6-3-2005

"Yes, I did send it to Scott and everyone else, but forgot to send it to you … sorry!

I also want to share with the team that I have, on occasion, received incorrect anatomic information from the French team during the course of this project. I have managed these situations by speaking with Axel Arnaud, MD and then proceeded. This is and has been a very challenging project for everyone, people will not be 100% accurate all of the time, so this is not a criticism. I just think it is important not to 'react' but to validate the information we receive from our customers.

…we are committed to integrity and excellence and have delivered a revolutionary tool throughout the world that will have a tremendous impact on the lives of many women!"

ETH.MESH.00029342, 6-3-2005, email from Ophelie Berthier to Kendra Munchel and others about SSL and distance from ischial spine for posterior trocar passage:

"Based on the latest conversation I just had with Kendra, + the follow up conversation I had with Pr Jacquetin after the meeting, Axel & Dr Debodinance after Jeff Levy's email to validate the sentence, we confirm that saying "The cannula-equipped guide passes through the subcutaneous tissues, then the dense fat of the ischioanal fossa, to the underside of the sacrospinous ligament, approximately 2cm cm [sic] medial to the ischial spine" is appropriate as there is the word "approximately" qualifying it. …"

[191] Prolift surgical technique document, under the heading of "Preparation for Placement of the Posterior Segment: "The Cannula-Equipped Guide is advanced until it is contact with the inferior side of the sacrospinous ligament approximately 3-4 cm medial to the ischial spine. …" (page 11, ETH.MESH.00419581)

through the sacrospinous ligament 2 cm medial to the ischial spine.[192] However, the narration also twice describes perforation of "the midportion of the sacrospinous ligament," without clarifying whether the "midportion" refers to the length or width of the sacrospinous ligament.[193] In another example of internal inconsistency, one of the surgical videos describes planned placement of the posterior cannula-equipped guide as 1-2 fingerbreadths medial to the ischial spine;[194] in the same video, placement on the patient's right side is described as 2 fingerbreadths while at the same time an anatomic inset depicts placement 2 cm medial to the ischial spine.[195] Obviously, measurements based on "fingerbreadths" will vary significantly from surgeon to surgeon and, as noted above, cannot possibly indicate the optimal placement for every individual patient. This introduces further risk.

"Tension-free" placement of the mesh implant and the mesh straps

Despite the frequent use of the term "tension-free" to describe mesh placement in the Prolift procedures, Ethicon acknowledges that there is no standardized objective means for a physician to determine whether Prolift mesh placement is in fact "tension-free."[196] In fact, Ethicon cannot even provide a working definition of this term, leaving only the ambiguous term "tension-free."

In addition, various documents, including surgical training videos, refer to "adjustment of tension."[197,198,199] If the setting is "tension-free," one would not adjust the level of tension. The

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[192] ETH.MESH.000001, Posterior Repair segment: Narration describes passage of the posterior cannula-equipped guide through the sacrospinous ligament 2 cm medial to the ischial spine (video time 1:58 to 2:06).

[193] ETH.MESH.000001, Posterior Repair segment: Narration describes passage of the posterior cannula-equipped guide to and through the midportion of the sacrospinous ligament (video time 00:23 to 00:29); and passage of the cannula-equipped guide perforating the midportion of the sacrospinous ligament (video time 2:07 to 2:15).

[194] ETH.MESH.000032, surgical video depicting posterior Prolift procedure, narration describes planned placement of the posterior cannula-equipped guide 1-2 fingerbreadths medial to the ischial spine (video time 5:37 to 5:42).

[195] ETH.MESH.000032, surgical video depicting posterior Prolift procedure, narration describes placement of the posterior cannula-equipped guide on the patient's right side as 2 fingerbreadths medial to the ischial spine, while an anatomic inset depicts placement 2 cm medial to the ischial spine (video time 6:12 to 6:21)

[196] Deposition testimony, David Robinson, 3-13-2012, Page 177, lines 19-25, and page 178, line 1
"Q. My question is, is there any statement in this surgical technique [document] that gives a physician some measure to understand whether or not they've achieved tension free so that they'll know what they're trying to achieve, some objective measure? A. No. We had no tool to objectively measure tension."
Deposition testimony, Paul Parisi, 506:11-21: "Q. You cannot state to me as you sit here right now an objective test or standard that a physician can utilize to ensure that, after placing a Prolift, that Prolift was placed in a proper tension-free manner. You can't give me a standard or a test for that. Correct? A. As I said, I'm not a medical doctor. As I sit here today, I can't recall information of that nature."

[197] Prolift surgical technique document: "Further fine adjustment of the tension and position of the Total Implant may be performed following closure of the vaginal incisions at the end of the procedure." ETH.MESH.00419584; ETH.MESH.00419585; ETH.MESH.00419592

[198] Prolift surgical technique document, heading of Vaginal Closure and Final Adjustment: "… The straps should be used to make any required additional fine adjustment to the Total Implant position, taking care to not place the mesh under tension." ETH.MESH.00419585; ETH.MESH.00419593; ETH.MESH.00419600

[199] Prolift surgical technique document: "… A further fine adjustment of the tension and position of the Posterior Implant may be performed following closure of the vaginal incisions at the end of the procedure." ETH.MESH.00419599

numerous contradictions as to "tension" or the lack thereof demonstrates a significant flaw in the design of the Prolift.

Even after more than 4 years of marketing and training with the Prolift procedures, Ethicon recognized the inadequacy of its training with regard to teaching the "tension-free" aspects of the Prolift procedure, and the fact that most surgeons did not even understand the concept.[200] Piet Hinoul confirmed this on September 3, 2009.[201] An even clearer example of Ethicon's knowledge that variations would occur is presented in an email from Ophelie Berthier to Giselle Bonet before the Prolift was released.[202]

Fixation of posterior straps using the transgluteal or vaginal approach

Two different approaches are offered by Ethicon for placement of the posterior mesh implant and straps. In one approach, two perineal incisions are made, one each on the right and left sides of the patient, and the cannula-equipped guides are passed through the gluteal area to traverse the sacrospinous ligament and exit into the vaginal incision. In the other approach, each of the 2 posterior straps is shortened and fixed directly to the sacrospinous ligament on each side.[203]

However, given these two surgical alternatives, the following unanswered questions arise:

How does the surgeon determine that sacrospinous fixation of the posterior Prolift straps is necessary or preferred over the transgluteal approach to placement of the posterior Prolift straps in a standardized way?

> Although Ethicon described these two surgical alternatives for the posterior Prolift procedure, it provided no guidance to surgeons as to how to choose one alternative over the other for an individual patient. Ethicon developed the posterior Prolift procedure with mesh straps to pass through the sacrospinous ligaments to maximize stability of the posterior mesh implant.[204] In fact, the Prolift surgical technique document emphasizes the essential nature of installing all of the mesh straps.[205] Indeed, it seems incongruous that Ethicon would recommend a variation that dispenses with the mesh straps providing critical support of the mesh implant at the vaginal apex. It seems possible that not using the mesh straps would lead to a higher likelihood of recurrent apical and posterior vaginal prolapse.

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[200] ETH-49659, email from Aaron Kikemo, 8-10-2009, summary of points of feedback from clinicians: "A real misconception exists in the community that leaving the cannuli in place until after the vaginal incisions are closed is to provide a means to TIGHTEN the arms. We need to really think about how to change our teaching to let people understand what post closure mesh tensioning means. …"

[201] ETH.MESH.00816396-00816398

[202] Exhibit 131/421

[203] Prolift surgical technique document: "An alternative approach is to directly fixate the Posterior Segment straps (6) to the superficial aspect of the sacrospinous ligament. This can be accomplished by trimming the distal portion of these straps to the proper length and performing fixation with suture or alternative fixation means." (page 12; ETH.MESH.00419582)

[204] Prolift surgical technique document: Heading, Mesh Fixation: "The implants are held in place by friction action on the associated straps passing through tissue. …" (page 2, ETH.MESH.00419572)

[205] Prolift surgical technique document: Heading, Mesh Fixation: "… It is essential to install all of the available mesh straps to properly place and secure the implants." (page 2, ETH.MESH.00419572)

Alternatively, placement of the mesh straps through the sacrospinous ligament and ischiorectal fossa plausibly increases the likelihood of complications in those areas. Nevertheless, Ethicon provides no evidence of equivalent safety and effectiveness for these two surgical alternatives.

How does the surgeon determine the proper length for trimming of the posterior straps in a standardized way?

Ethicon provided no guidance to the surgeon for determining the proper length to trim the posterior Prolift mesh straps if the surgical alternative of sacrospinous fixation of the Prolift mesh straps is chosen. In addition, the expected extent of Prolift mesh contraction was not described at any point in the Prolift IFU or surgical technique document. If the posterior Prolift mesh straps are trimmed too short, Prolift mesh contraction may detach or distort the Prolift mesh straps' attachment to the sacrospinous ligament, increasing the risk of recurrent prolapse and complications such as pelvic pain due to Prolift mesh tension on nearby muscles and nerves. If the posterior Prolift mesh straps are left too long, Prolift mesh redundancy increases the foreign body load and subsequent inflammatory reaction; Prolift mesh folding or wrinkling due to Prolift mesh redundancy may increase the risk of vaginal mesh exposure. Scott Ciarrocca testified in the context of the design assessment to knowing the risk of the Prolift mesh folding or bunching. However, other than resulting erosion and recurrence, he could not identify other consequences, instead deferring to medical affairs for an opinion regarding the consequences.[206]

How does the surgeon determine the optimal means of fixing the shortened posterior Prolift straps to the sacrospinous ligaments in a standardized way?

Ethicon provided no guidance to surgeons as to the optimal means of fixing the shortened posterior straps to the sacrospinous ligaments. Among the options available for this fixation (for example, direct suture fixation or fixation with a suturing device), Ethicon provided no evidence of equivalent safety and effectiveness among these different options for fixation. Performing the posterior Prolift procedure using this technique introduces an unreasonable element of variability that will directly influence the outcomes in terms of safety and effectiveness.

Positioning of the anterior segment of the Prolift mesh implant

The anterior segment of the Prolift mesh implant is intended to be placed under the bladder in lateral contact with the arcus tendineus fascia pelvis (ATFP).[207] However, the Prolift surgical technique document gave no guidance as to how to accomplish this step in a standardized way, raising the following unanswered questions, which, as with all of the unanswered questions and

[206] Scott Ciarrocca dep., 454:16-547:20

[207] Prolift surgical technique document: "Optimally, the Anterior Segment of the Total Implant will be positioned tension-free under the bladder while ensuring lateral contact against the ATFP. Lateral contact of the Total Implant to the ATFP should be carefully verified." (page 14; ETH.MESH.00419584)

lack of guidance discussed in this report, further illustrate the unnecessary and dangerous nature of the Prolift procedure:

- How does the surgeon determine that "tension-free" positioning of the anterior segment of the Prolift mesh implant has been attained in a standardized way?
- How does the surgeon "carefully" verify that the anterior segment of the Prolift mesh implant is in lateral contact with the ATFP in a standardized way?
- If the anterior segment of the Prolift mesh implant is not in lateral contact with the ATFP, how does the surgeon address this in a standardized way?
- If the anterior segment of the Prolift mesh implant is not positioned "optimally," how does the surgeon address this in a standardized way?
- What are the consequences for the patient if this is not achieved?

Positioning of the posterior segment of the Prolift mesh implant

The posterior segment of the Prolift mesh implant is intended to be placed above the rectum in lateral contact with the superior surface of the levator ani muscles.[208] However, the Prolift surgical technique document gave no guidance as to how to accomplish this step in a standardized way, raising the following unanswered questions:

- How does the surgeon determine that "tension-free" positioning of the posterior segment of the Prolift mesh implant has been attained in a standardized way?
- If the posterior segment of the Prolift mesh implant is not in place with its lateral edges against the superior surface of the levator ani muscles, how does the surgeon address this in a standardized way?
- If the posterior segment of the Prolift mesh implant is not positioned "optimally," how does the surgeon address this in a standardized way?
- What are the consequences for the patient if this is not achieved?

Reducing the size (trimming) of the Prolift mesh implant

In two places, addressing the placement of the anterior and posterior segments of the Prolift mesh implant, the Prolift surgical technique guide recommends reducing the size of (trimming) the mesh implant.[209] However, the Prolift surgical technique document gave no guidance as to how to accomplish trimming the mesh implant in a standardized way, raising the following unanswered questions:

How does the surgeon determine whether trimming of the anterior and posterior mesh implants is "required" in a standardized way?

How does the surgeon determine the magnitude of "small reductions" needed for the anterior and posterior mesh implants in a standardized way?

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[208] Prolift surgical technique document: "Optimally, the Posterior Segment of the Total Implant will be positioned tension-free above the rectum with its lateral edges against the superior surface of the levator ani muscles." (page 15; ETH.MESH.00419585)

[209] Prolift surgical technique document: "If required, small reductions in the dimensions of the Total Implant to ensure proper fit should be performed at this point." (page 14; ETH.METH.00419584) "Minor reductions in Total Implant length should be made at this point, if required, to ensure proper fit." (page 15; ETH.MESH.00419585)

How does the surgeon determine "proper fit" of the anterior and posterior mesh implants in a standardized way?

Ethicon received feedback from experienced Prolift surgeons that it is especially important to consider how much the mesh is expected to contract when determining whether and how much mesh trimming to perform.[210] Yet, Ethicon failed to address this issue at all in the Prolift IFU, the Prolift surgical technique document, or Prolift professional education, the interrelationship between mesh contraction (shrinkage) and trimming of the mesh, in affecting patient outcomes.

Adjusting the position and tension of the Prolift mesh implant after closing vaginal incisions

In two places, addressing the placement of the anterior and posterior segments of the Prolift mesh implant, the Prolift surgical technique guide recommends further adjustments of the tension and position of the Prolift mesh implant after the vaginal incisions are closed.[211] In addition, the Prolift surgical technique guide recommends using the straps to make additional adjustments of the position of the Prolift mesh implant.[212]

However, the Prolift surgical technique document gives no guidance as to how to determine whether further adjustments of the tension and position of the Prolift mesh implant is necessary and how to determine the magnitude of further adjustments of the tension and position of the Prolift mesh implant in a standardized way. More than 4 years after Prolift was launched, Ethicon was aware of the difficulty of teaching "tension-free" mesh placement in a standardized way.[213] This raises the following unanswered questions:

- If tension-free positioning had been attained at the previous steps, why would "further fine adjustments of the tension and position" of the anterior and posterior segments and the mesh straps of the Total Implant be necessary after the vaginal incisions have been closed at the end of the procedure?
- Given that the vaginal incisions are closed and the Prolift mesh implant is no longer visible at this point, how does the surgeon determine whether "further fine adjustments" of the anterior and posterior segments and the mesh straps of the Total Implant are needed in a standardized way?

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[210] 12-1-2005, ETH-80641, Notes from Prolift roundtable discussion with experienced Prolift surgeons:

- "Mesh will contract by up to 30%.
- If you measure the vaginal length and trim to size, [the] mesh will contract and possibly cause dyspareunia. Therefore always leave loose and tension free.

[211] Prolift surgical technique document: "Further fine adjustments of the tension and position of the [anterior segment of the] Total Implant may be performed following closure of the vaginal incisions at the end of the procedure." (page 14; ETH.MESH.00419584) "Further fine adjustments of the tension and position of the [posterior segment of the] Total Implant may be performed following closure of the vaginal incisions at the end of the procedure." (page 15; ETH.MESH.00419585)

[212] Prolift surgical technique document: "The straps should be used to make any required additional fine adjustment to the Total Implant position, taking care to not place the mesh under tension." (page 15; ETH.MESH.00419585)

[213] ETH-49659, email from Aaron Kikemo, 8-10-2009, summary of points of feedback from clinicians: "A real misconception exists in the community that leaving the cannuli in place until after the vaginal incisions are closed is to provide a means to TIGHTEN the arms. We need to really think about how to change our teaching to let people understand what post closure mesh tensioning means. …"

- Given that the vaginal incisions are closed and the implant is no longer visible at this point, how can the surgeon determine that "further fine adjustments" of the anterior and posterior segments and the mesh straps of the Total Implant have been performed correctly in a standardized way?

Impact of Implantation, Adjustment and Pelvic Forces on Mesh Characteristics Such as Pore Size

Ethicon made no effort to determine how the Prolift mesh would be affected by the process of implantation and adjustment, or how the normal pelvic forces would impact the properties of the Prolift mesh, for example, the impact of Prolift mesh implantation on the pore sizes, elasticity, susceptibility to fibrotic bridging, and scar tissue formation.

VII. The Prolift Procedure Introduced Novel Risks and Difficulties

The Prolift Systems represented not only a complex pre-cut surgical mesh with dedicated single use instruments, but also a new surgical procedure that was different from traditional vaginal prolapse surgery in material ways. These marked differences were reflected in feedback from surgeons involved in Prolift product evaluations before Prolift was commercially available.[214]

The feedback from the first TVM training course in Lille, France shows that Ethicon knew the Prolift to be very different from other products and procedures, which emphasized the need for specialized training.[215]. In addition, these differences were reflected in feedback from surgeons experienced in using Prolift after Prolift was marketed.

Ethicon Knew of All Risks of the Prolift Prior to Marketing the Prolift

Piet Hinoul testified that Ethicon knew all the risks and adverse reactions that could occur with the Prolift before Ethicon began to market the Prolift. (Piet Hinoul Dep. Tr. 480:8-13). Piet Hinoul acknowledged these risks, and that they were not stated in Ethicon's warnings and information about the Prolift, claiming (unreasonably) that surgeons who would perform this new, revolutionary procedure, would simply know or figure them out..[216] For example, with regard to the risk known to Ethicon, "that a young, sexually active woman could suffer from painful sexual intercourse and the inability to have normal pleasurable sexual relations on a long-term basis as a

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[214] ***Prolift Product Evaluation, 2-7-2005:***

Comment in Product Evaluation Results: "Participant indicated that the implant and delivery system was not suitable for his current technique but that he would need to learn a new technique to perform this repair." (ETH-01624)

[Ethicon] Response in Product Evaluation Results: "Clearly for most physicians the Prolift procedure will be a deviation from what they are currently doing." (ETH-01624)

[215] ETH.MESH.02282833-02282834.

[216] This was echoed by Aaron Kirkemo (231:16-233:13) and Marty Weisberg (120:21-121:11 rough).

result of the Prolift," after admitting that the risk is not stated in the IFU, Piet Hinoul said that risk would be known nonetheless..[217]

However, Ethicon had no way of "making sure" that the Prolift product and procedure were only used by experienced pelvic floor surgeons. Moreover, experienced pelvic floor surgeons are not necessarily experienced in specific aspects of transvaginal mesh surgery; by definition, no surgeon had experience with the Prolift procedure at its launch because it was a new procedure that differed markedly from traditional non-mesh, non-trocar-based vaginal prolapse surgery. Nevertheless, this assumption was given with regard to multiple serious risks known to Ethicon, not specifically stated in the Prolift IFU, for example contraction leading to permanent pain, contraction of the Prolift mesh that can lead to chronic pain and the chronic inability to have pleasurable sexual relations, shrinkage of the mesh could lead to chronic debilitating pain that could not be successfully treated through follow-up operations or any treatment and that the woman could be left despite multiple interventions with permanent chronic pain.[218]

Once Ethicon sold the Prolift product to a hospital, Ethicon had no control over which surgeons used the Prolift product. At Prolift launch, some at Ethicon may have said they intended to restrict access to Prolift to surgeons experienced in pelvic floor surgery, but in fact, this could not be accomplished in practical terms; as confirmed in deposition testimony, Ethicon was well aware of that fact.[219] Second, it was unreasonable to expect even highly skilled surgeons to know of all the potential complications of the Prolift product and procedure simply because they are pelvic floor surgeons. Surgeons expect to be thoroughly and explicitly warned regarding the risks of a medical device and procedure such as the Prolift product and procedure. Ethicon's expectation that surgeons would know or figure out significant risks known to Ethicon, without being told, was completely unreasonable. The Prolift system was a revolutionary procedure, according to Ethicon,[220] with a newly designed delivery system and a large, uniquely shaped permanent mesh implant.. Sean O'Bryan of regulatory affairs confirmed that it is not proper to fail to disclose risks

[217] Hinoul dep., 328:22-329:23
[218] Hinoul dep., 329:5-9; 329:13-330:1; 330:2-330:23; 333:20-334:12; 336:11-338:12.
[219] Robinson dep., 376:15-379:6
[220] ETH-00761, cooperative Prolift advertising directed to patients that can be personalized with a doctor's name, address, and logo: "It's a new and revolutionary surgical procedure called Gynecare Prolift Pelvic Floor Repair System."
ETH.MESH.00011654, Prolift patient brochure: "Gynecare Prolift Pelvic Floor Repair System, a revolutionary surgical technique that offers promising results for women with pelvic organ prolapse…"
ETH.MESH.00016663, Prolift patient brochure, heading What is Gynecare Prolift? "A revolutionary surgical procedure using Gynecare Prolift employs a specially designed supportive soft mesh placed in the pelvis to restore pelvic support …"

based on an assumption that the risk would be known and fully understood by the surgeon using the device.[221]

Other Risks Described by Piet Hinoul:

Pore size and effective porosity are critical to the safety and effectiveness of a permanent synthetic mesh implant. Yet, Clifford Volpe testified that he was not aware of "any testing ever done within Ethicon to determine the effective pore size in actual use for the Prolift…" [222] It was critical that Prolift mesh porosity be sufficient to cause necessary tissue ingrowth, comprised of the healthy, vascularized tissue necessary to safely incorporate the mesh, along with only that amount of fibrotic tissue needed to secure the mesh in place. That desired level of fibrotic tissue was referred to by Piet Hinoul as a "scar net," not an unsafe, excessive amount of fibrotic tissue, that would be unsafe for patients. Piet Hinoul described this as a necessity of the design[223]

The consequences of fibrotic bridging can be severe (see also sections on mesh contraction, mesh roping, and banding/ridging of Prolift mesh). This was described by Piet Hinoul in the context of an Ethicon science presentation about the need for a 1 mm effective pore size, which was attended by David Robinson among others.[224] Piet Hinoul attended a meeting with Professor Klosterhalfen, who he referred to as "the God of surgical pathology on the subject of textile implants in the solar system," where the need for 1 mm pore size was made clear.[225, 226]

Ethicon did not act on its knowledge that the pores of the mesh needed to be at least 1 mm to be safe. The claim that the Prolift had sufficient porosity is simply wrong. Moreover, Ethicon did not disclose the known frequency, extent, and severe consequences of the intense, chronic foreign body reaction and excessive fibrosis caused by the inadequate Prolift mesh pore sizes. Ethicon also failed to warn of the fact that the Prolift mesh pores would "collapse" when placed under force with implantation, further impairing the ability of the mesh to safely integrate with the body's tissue (see discussion of Project Thunder, and Ethicon's recognition of the need for larger pores and stress shielding).

Risks of Contraction:

[221] O'Bryan dep., 106:16-107:21 rough
[222] Clifford Volpe dep., 361:1-8
[223] Hinoul dep., 176:4-13; 180:8-19; 181:8-15; 209:21-210:14
[224] Hinoul dep., 571:13-22; 572:16-574:9; 574:19-23; 577:7-10
[225] Hinoul dep., 582:19 – 583:5
[226] Hinoul dep., 583:25-584:13, 584:19-587:4

Ethicon incorrectly advised physicians that, "The mesh remains soft and pliable, and normal wound healing is not noticeably impaired."[227] To the contrary, Axel Arnaud admitted the mesh does not remain soft in actual use, and that this is no more than illusion.[228] Instead, the mesh becomes hard, firm, and contracted, introducing significant risks and clinical consequences to patients admitted by Piet Hinoul.[229] A related risk and consequence of the Prolift mesh was the extensive, dangerous surgery that could be necessitated to try to remove the Prolift mesh, described, for example, by Piet Hinoul..[230] Further, Piet Hinoul admitted that severe complications could not be treated by all surgeons, but rather only by the most skilled, experienced surgeons, if at all.[231] This litany of severe risks, all of which were known to Ethicon from the start, render the Prolift device and procedure medically unsafe, and renders the risk benefit profile unacceptable.

In fact, in 2004, Ethicon scientist Gene Kammerer authored a powerpoint regarding a Project to develop a treatment of prolapse that would allow natural tissue to regenerate in a natural and physiologic way. (ETH.MESH.01217421). On the first page of the powerpoint, titled: Clinical Challenges, Mr. Kammerer points out: (1) mesh implants produce a high level of scar formation," (2) scar tissue is hard, non-elastic, contracts and can lead to post-operative complications, and (3) a need exists for a mesh which does not produce scar or adhesion formation and provides a strong long lasting support." These are all strong reasons why Ethicon knew the safety profile for the Prolift mesh was medically unacceptable. Even more to the point, in an April 6, 2001 powerpoint presentation regarding a project to explore the use of Vypro for pelvic floor repair, the use of Prolene Soft mesh for pelvic floor repair was rejected – since voice of customer reported the mesh was too stiff for use in vaginal tissues, and the team recommendation was "Do not pursue." (Laura Angelini Dep. Tr., June 19, 2015).

Because of the differences between the Prolift procedures and traditional vaginal prolapse surgery as set forth above, Ethicon internally recognized the need for surgeons of even high skill levels to undertake specialized training. Instead of strongly warning of the need to be trained, Ethicon merely recommended training for surgeons planning to perform the Prolift procedures, and surgeons were not required to attend training or to demonstrate any level of proficiency before performing the Prolift procedures. Ethicon made no formal effort to evaluate physicians' skill during or after training, or to limit the use of the Prolift to the most skilled physicians (as they recognized to be a necessity). This added to the unnecessary risks introduced by the Prolift.

In deposition testimony, Paul Parisi, director of professional education at Ethicon, testified to the intended high level of skill for surgeons using the Prolift, and confirmed that a system of

[227] ETH.MESH.02341734
[228] Arnaud dep, 68:18-69:13
[229] Hinoul dep., 382:9-393:3, 518:24-519:21
[230] Hinoul dep., 509:22-510:22
[231] Hinoul dep., 147:21-149:9

"checks and balances" was instituted to ensure that only the highly skilled surgeons could get trained.[232] Feedback from experienced Prolift surgeons recommended implementation of evaluation of surgeons and "stage gates" to be satisfied before being certified on the procedure.[233] Ethicon ignored this recommendation, and internal documents show that preceptors complained to Ethicon that doctors lacking the necessary skill and knowledge were being invited to the training by the sales department.

The Prolift Training Source Materials

Prolift IFU

The Prolift IFU states that "Training on the use of the Gynecare Prolift Pelvic Floor Repair Systems is recommended and available."[234] Draft versions of the Prolift IFU contained much stronger wording, under the heading of "Warning," as to the need for training with the Prolift Systems.[235] However, final versions of both the original and subsequent revised Prolift IFUs carry only the statement above.

In contrast, the IFUs for Ethicon products and techniques that were much less complex than the Prolift Systems to perform carried stronger recommendations for training than the Prolift IFU. These products and techniques included the TVT[236] and the TVT-O[237] products and techniques for the treatment of stress urinary incontinence.

The Prolift IFU does not contain detailed instructions on performing the Prolift procedures. Instead, Ethicon decided that detailed instructions should be placed in a separate document.[238] Although the stated intent of this separation was "to encourage users to seek appropriate training," it was foreseeable that the exact opposite would occur in some cases. The surgical technique guide was not placed in the Prolift kits, as the IFU was, and could only be obtained from an Ethicon sales representative or presumably at training sessions if requested. Since Ethicon did not require training, did not evaluate trainees, and had no way of restricting access to the Prolift kits to certain surgeons once the kits were sold to a hospital, surgeons could use the Prolift kits without ever

[232] Paul Parisi dep., 766:15-789:25.
[233] ETH.MESH.01184121
[234] ETH-00002
[235] ETH-62793, 9-8-2004, draft Prolift IFU: "WARNING: It is strongly recommended not to attempt to use this device without training. Contact your company sales representative to arrange the appropriate education."
[236] TVT IFU, ETH.MESH.02340331: "Important: … The device should be used only by physicians trained in the surgical treatment of Stress Urinary Incontinence and specifically in implanting the TVT device. …"
[237] TVT-O IFU, ETH.MESH.02340830: "Important: … The device should be used only by physicians trained in the surgical treatment of stress urinary incontinence and specifically in implanting the Gynecare TVT Obturator device. …"
[238] ETH-06230, 8-26-2004: "The Project D'Art team has decided that detailed surgical teachings on the D'Art procedures shall be captured in a document package separate from the required safety information in the product Instructions for Use (IFU). Separation of this material from the IFU is intended to encourage users to seek appropriate training on these procedures. The IFU shall include a recommendation to seek this training through established Gynecare Professional Education programs. These programs will provide users with a more comprehensive understanding of the D'Art procedures, associated anatomy, and appropriate surgical techniques than could otherwise be conveyed in the IFU."

having seen the Prolift surgical technique guide, or demonstrating knowledge of the contents or proficiency with the Prolift procedure.

Prolift surgical technique guide[239]

The Prolift IFU refers to the Prolift surgical technique guide for further information on the Prolift procedures.[240] As described above, the Prolift surgical technique document offers numerous variations, and options within these variations, without adequate instructions as to certain aspects of the procedures.

Prolift Procedural Videos and Presentations

In addition to the Prolift IFU and the Prolift surgical technique document, Ethicon developed procedural videos for training purposes. These include procedural videos and presentations, as follows:

1) **Presentation titled: "Meshes for Incontinence and Pelvic Floor Repair"** by Axel Arnaud, M.D. (Scientific Director, Europe Gynecare).[241] The presentation is approximately 28 minutes in duration. Although the date of the presentation was not stated, Dr. Arnaud referred to the present time as the year 2002.

Summary of Content

This video addressed different characteristics of synthetic meshes for use in incontinence and vaginal prolapse surgery. The stated objective of the presentation was to help surgeons make choices with regard to the different meshes.

Comments on Content

1. This presentation was clearly biased and promotional to Gynecare products, specifically the Gynecare TVT for incontinence surgery and Gynemesh PS mesh for vaginal prolapse surgery.
2. Dr. Arnaud stated that a requirement common to meshes used in incontinence and vaginal prolapse surgery was that the mesh must not shrink. Dr. Arnaud recommended that the surgeon choose a lightweight polypropylene mesh to meet this requirement. However, so-called lightweight polypropylene meshes including Gynemesh PS mesh do not meet this requirement as they are well known to shrink significantly.
3. Dr. Arnaud stated that "We have developed lighter meshes specifically for your use in urogynecology." This is untrue; Gynemesh PS mesh is the exact same mesh as Prolene Soft mesh, used by general surgeons in hernia repair.

[239] ETH.MESH.00419571-00419600
[240] Prolift IFU, ETH-00002: "Refer to the recommended surgical technique for the Gynecare Prolift Pelvic Floor Repair Systems for further information on the Gynecare Prolift procedures."
[241] ETH.MESH.PM.000011

4. Dr. Arnaud stated that a requirement common to meshes used in incontinence and vaginal prolapse surgery was that the mesh must be histologically well tolerated, and he recommended that the surgeon choose an inert material to meet this requirement. Dr. Arnaud stated that there was "no scientific evidence to use something else than polypropylene," implying that polypropylene meets this requirement by being inert. However, polypropylene is not inert; scientific evidence indicates that it undergoes chronic degradation and stimulates a long-lasting, if not permanent, inflammatory and foreign body reaction.
5. The presentation identified several requirements for meshes used in incontinence and vaginal prolapse surgery. However, comparisons and conclusions were not based on what would be optimal in clinical practice, but instead were based only on what meshes were currently available. For example, Dr. Arnaud concluded that Gynecare TVT has optimal elasticity, only because the TVT mesh distends more at lower force loads, compared with IVS, Sparc, and Gore-Tex meshes.
6. Dr. Arnaud presented no data specific to the requirements of optimal friction and optimal elasticity for mesh used in vaginal prolapse surgery. Dr. Arnaud recommended that the characteristics of the Gynecare TVT be used as a reference, because the TVT has long-term results. However, this recommendation is problematic for several reasons. First, the Gynecare TVT mesh is not the same as the Gynemesh PS mesh. Second, the demands placed on mesh used in incontinence versus vaginal prolapse surgery are very different, and it cannot be assumed that the characteristics of TVT mesh are automatically the necessary or optimal characteristics for mesh used in vaginal prolapse surgery. Third, the shape, surface area, and mesh strap implantation points differ dramatically between the TVT procedure for incontinence and the use of Gynemesh PS mesh for vaginal prolapse. Moreover, the stresses placed on the two meshes for their different clinical indications are considerably different and not directly comparable. This seems like another example of Ethicon's practice to take shortcuts and unreasonably assign attributes from one mesh to another, despite marked dissimilarities in their intended use. Far better would be to specifically study the requirements of friction and elasticity in meeting the needs for vaginal prolapse surgery and then determine whether Gynemesh PS mesh met those needs, rather than making unwarranted assumptions based on the TVT mesh product and procedure.

2) **Prolift Procedure Videos**[242]

This video includes edited and narrated Prolift procedures, Uterine Conservation/Total Repair and Vaginal Hysterectomy/Total Repair/TVT-O. There appears to be 2 copies of the 2 procedures. This appears to be the same video and narration as shown in the Procedure Videos segment of ETH.MESH.PM.000001 (without the other 4 segments).

3) **Prolift Interactive Training Module**[243]

[242] ETH.MESH.PM.000039, created 8-22-2011
[243] ETH.MESH.PM.000037, created 5-25-2011

This appears to be exactly the same as ETH.MESH.PM.000001, including the original Prolift IFU, and not the revised Prolift IFU after FDA review. Even considering that the revised Prolift IFU wasn't available until 1-½ years after the FDA review was completed, Ethicon failed to include the revised Prolift IFU with this training module that was completed in May 2011, approximately 2-½ years after the revised Prolift IFU became available. This means that surgeons viewing this training module will be unaware of the substantial changes in the Prolift IFU,, including the addition of several contraindications, warnings, and precautions that provide important information about risks, complications, and adverse events due to the Prolift procedure and permanent Prolift mesh implantation (even though the revised Prolift IFU still has substantial limitations and inaccuracies).

4) **Prolift Technique and Procedure Video**[244]

The video has 5 major segments: Introduction, Anatomic Considerations, Procedure Videos, Surgical Technique, and Prolift IFU. The first 3 segments are narrated videos with a total duration of approximately 53 minutes. The scripts of the narrations are presented as sidebars to the videos, although the narration varies slightly from the scripts for the Anatomic Considerations and Procedure Videos segments. The Surgical Technique segment provides the text of the Prolift surgical technique document.[245] The IFU segment provides the text of the original Prolift Instructions for Use (IFU).

Introduction: The video is a stylized three-dimensional depiction of pelvic anatomy with the Prolift mesh implant in place. The narration is approximately 1 minute in duration. The narration states that "Gynecare Gynemesh PS is a soft pliable polypropylene material intended to reinforce weakened rectovaginal fascia and visceral connective tissues that surround the vaginal epithelium in the patient with pelvic floor prolapse." The sidebar with text includes the Indication statement for the Prolift Systems and a brief description of product and procedure development.

Anatomic Considerations: There are 4 segments: Anterior Anatomy, Anterior Repair, Posterior Anatomy, and Posterior Repair, for a total duration of approximately 17 minutes. The segments depict stylized three-dimensional pelvic anatomy.

1. The Anterior Anatomy segment (approximately 3 minutes) describes anatomy of anterior vaginal support, including the muscles, fascial structures, and bony attachments. The obturator foramen is described, along with the obturator nerve and branches, and the obturator vessels and branches.
2. The Anterior Repair segment (approximately 6 minutes) describes placement of the anterior mesh implant, with description of the structures that the superficial and deep anterior cannulas pass through and location of the obturator nerve and blood vessels. The end of the superficial anterior mesh arm (#4) is incorrectly depicted as having a rounded end, rather than the correct squared end. The anterior repair segment does not describe or depict the location of the pudendal nerve and blood

[244] ETH.MESH.PM.000001, created 2-14-2005
[245] ETH.MESH.00419571-600

vessels, which are at risk for injury during passage of the deep anterior cannula-equipped guide.

3. The Posterior Anatomy segment (approximately 4 minutes) describes anatomy of posterior vaginal support, including the muscles and fascial structures. The narration and visual aids describe the height of the perineal body as 3-4 cm; however, the sidebar text describes the height of the perineal body as 2 cm.
4. The Posterior Repair segment (approximately 4 minutes) describes placement of the posterior mesh implant, with description of the structures that the posterior cannulas pass through, and location of the pudendal nerve and its branches and pudendal blood vessels and branches. This segment narrates and demonstrates placement of the posterior cannula-equipped guide 2 cm medial to ischial spine; however, the surgical technique document states that the posterior cannula-equipped guide should be placed approximately 3-4 cm medial to the ischial spine. This is a critically important contradiction, because of the vital structures at risk for damage during placement of the posterior cannula-equipped guide through the sacrospinous ligament. Near the origin of the sacrospinous ligament and coccygeus muscle at the ischial spine, the pudendal nerve and blood vessels pass behind the ischial spine. Near the insertion of the sacrospinous ligament and coccygeus muscle at the lateral border of the coccyx and most caudad segment of the sacrum, the inferior gluteal nerve and blood vessels pass over the upper posterior edge of the sacrospinous ligament.

Procedure Videos: There are 2 segments, Uterine Conservation/Total Repair and Vaginal Hysterectomy/Total Repair/TVT-O, for a total duration of approximately 35 minutes. These segments depict edited and narrated versions of Prolift surgical procedures. Scripts of the narration are provided to the left of the video screen with a scroll bar; the scripts do not advance automatically with the narration.

1. Uterine Conservation/Total Repair
   The video is approximately 18 minutes. The section of the Prolift surgical technique document, Total Repair with Uterine Conservation[246] identifies 5 important differences[247] compared with the procedure described in full, Total Repair with Vaginal Hysterectomy.[248] Because the Total Repair with Uterine Conservation procedure does not spell out all steps of the procedure and does not indicate the order of the 5 different steps relative to the overall procedure, it is difficult to understand where the 5 different steps fit into the overall procedure.

2. Vaginal Hysterectomy/Total Repair/TVT-O

[246] Page 16 of the Prolift surgical technique document, ETH.MESH.00419586
[247] The 5 different steps are: 1) Implant preparation; 2) Anterior vaginal incision; 3) Anterior mesh fixation; 4) Posterior vaginal incision; and 5) Posterior mesh fixation.
[248] pages 5-15 of the Prolift surgical technique document, ETH.MESH.00419575-585

The video is approximately 17 minutes. The procedural steps for the total Prolift procedure are described in the Prolift surgical technique document, Total Repair with Vaginal Hysterectomy.[249]

The video also depicts TVT-O sling placement.

- The video describes and depicts that "The surgeon manipulates the skin of the medial thigh so that the [TVT-O] passer exits through the same skin incision used for the superficial strap [of the anterior Prolift mesh implant]."

  The Prolift surgical technique document provides no information on key aspects of the sling procedure when performed in conjunction with the Prolift procedure, including:

  - Whether to use the same skin incisions for the 2 sling straps as those used for the 2 superficial anterior Prolift mesh arms, or to make 2 separate skin incisions for the 2 sling straps;
  - When exactly in the course of the Prolift procedure that the sling procedure should be performed, particularly in relation to anterior Prolift mesh placement and removal of the 4 anterior Prolift cannulas;[250]
  - Which technique of placement of the sling should be used, either the "inside-out" or "outside-in" technique, to avoid displacing the superficial anterior mesh arms of the Prolift implant.[251] This is a critically important distinction, as emphasized by Ethicon in its first training session for Prolift preceptors,[252] yet the Prolift surgical technique document does not provide this information.
- The video describes and depicts a standardized means of "tension-free" placement of the TVT-O mesh: "0.5 cm of Gynecare TVT Obturator System tape is looped and grasped with an Allis clamp in this technique in order to position the tape underneath the urethra without tension."

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[249] Pages 5-15 of the Prolift surgical technique document, ETH.MESH.00419575-585

[250] ETH-02711, undated, feedback from experienced Prolift surgeons, under the heading of Concomitant Procedures: "… sling procedures accompany Gynecare Prolift System in the majority of cases for both manifest stress incontinence as well as treating occult incontinence. TVT-O is employed without difficulty but it is recommended that the cannulae stay in place while the sling is passed to avoid displacing the other mesh. The sling is generally done second and is adjusted after the prolapse is reduced after restoration of the apical and anterior wall anatomic relationships."

[251] Prolift launch strategy, November 11-12, 2004 training, ETH.MESH.00129575: competitive positioning: "TVT-O [tension-free vaginal tape – obturator; transobturator sling] for complete system – 'In out' [trocar and mesh placement from the vaginal incision to the obturator skin incision] for use with TVM patients – not to disrupt arms of mesh"

Rebuttals regarding competing products, ETH.MESH.00129382: "Even post TVM a TVT-O [tension-free vaginal tape – obturator; transobturator sling] "In-Out" [trocar and mesh placement from the vaginal incision to the obturator skin incision] is the best method to place a TVT. The In-Out helps to avoid disrupting any placed TVM straps."

[252] ETH.MESH.02282833, 10-7-2004, email TVM first training, key learnings: "A key learning has been the opportunity for leverage of TVT-O. In Cases requiring a TVT like surgery with prolapse it became evident that In-Out is the only safe way to perform a TVT after this procedure due to 'congestion' of the Ob [obturator] hole with mesh straps. Out-In may cause disruption of the mesh and complications – WE must show at least one TVT-O explaining this fact."

In contrast to the standardized technique used for "tension-free" placement of the TVT-O mesh, no such standardized technique exists for placement of the much larger Prolift mesh implant with 6 mesh arms.

5) **Video of the Prolift Procedure**[253]

The edited video depicts a total Prolift procedure for posthysterectomy vaginal vault prolapse, performed by Vincent Lucente, M.D. The duration of the video is approximately 9 minutes. Although a few comments are made during the procedure, the video is not formally narrated, and a script is not provided.

After placement of the posterior cannula-equipped guide and removal of the guide, only the cannula hub is visible at the posterior skin incision, and the distal end of the cannula in the posterior vaginal dissection is not visible. Since the posterior cannula-equipped guide must pass through the entire thickness of the fat-filled ischiorectal fossa, pass through the sacrospinous ligament and exit the posterior vaginal dissection, this suggests that the cannula and guide may not be long enough for certain obese patients.

6) **Prolift Animation With and Without Text**[254]

There are 4 segments: Prolift animation with text, Prolift animation without text, chapters with text, and chapters without text. The Prolift animation with text segment is approximately 4 minutes in duration and includes a brief text description of pelvic organ prolapse, followed by stylized two-dimensional images that depict normal pelvic anatomy, cystocele and Prolift mesh placement; rectocele and Prolift mesh placement; and uterine prolapse and Prolift mesh placement. The Prolift animation without text segment is approximately 3 minutes in duration and provides the same prolapse description and anatomic depictions as the Prolift animation with text segment, except for the absence of labels on the anatomic structures. The segments of chapters with and without text appear to be the same, and include the same prolapse description and anatomic depictions as single images.

7) **"Anatomic Landmarks During Transvaginal Placement of Mesh for Repair of Anterior Pelvic Support Defects"**[255]

The title slide of the video names Vincent Lucente, M.D. and James Raders, M.D. The video is approximately 10 minutes. The video presents an edited and narrated anterior Prolift procedure with laparoscopic visualization of anterior pelvic anatomy; the script of the narration is not provided. Note that laparoscopy would not normally be performed concomitantly with the Prolift procedure, unless there was a separate clinical indication for which laparoscopy was required. This video was apparently prepared as a teaching aid; visualization of anatomic structures as depicted in this video would not normally be available to a surgeon performing the Prolift procedure.

[253] ETH.MESH.PM.000058, created 2-14-2005
[254] ETH.MESH.PM.000027, created 12-14-2005
[255] ETH.MESH.PM.000057, created 1-28-2006

8) **"Laparoscopic Demonstration of Anatomic Transvaginal Placement of Mesh for the Repair of Anterior Compartment Defects"**[256]
The title slide of the video names Vincent Lucente, M.D. and James Raders, M.D. The video is approximately 10 minutes. The video and narration are the same as ETH.MESH.PM.000057, the only difference being the addition of arrows and other labeling techniques for the identification of pertinent landmarks and points of emphasis.

9) **Prolift Procedural Video**[257]
This video contains 4 segments with a total duration of approximately 54 minutes: Gynecare Prolift videos, IFU, Surgical Technique, and Video Scripts. The Gynecare Prolift videos are edited and narrated videos of 4 Prolift procedures, including an anterior Prolift procedure (narrated by Dr. Vincent Lucente), a posterior Prolift procedure (narrated by Dr. Vincent Lucente), a total Prolift procedure with uterine conservation (narrated by Dr. Jaime Sepulveda), and a total Prolift procedure for posthysterectomy vaginal vault prolapse (narrated by Dr. Jaime Sepulveda). The IFU segment provides the text of the original Prolift Instructions for Use (IFU). The Surgical Technique segment provides the text of the Prolift surgical technique document.[258] The Video Scripts, in a different segment, cannot be viewed at the same time as the Gynecare Prolift videos.

While describing adjustment of anterior mesh position and tension during the anterior Prolift procedure, the narrator states that "the biggest clinical challenge is post implant comfort."

The Video Scripts are poorly edited and contain numerous misspellings and misstatements, such as:

- "four finger" instead of "forefinger"
- "saw" instead of "soft"
- "ungulation" instead of "undulation"
- "ureterovesical" instead of "urethrovesical"
- "peritoneal defect" during anterior hydrodissection
- "unnecessarily" instead of "necessarily"
- "tendon" instead of "tends to"
- "never" instead of "now we're"

10) **Prolift Procedural Video**[259]
This appears to be exactly the same as ETH.MESH.PM.000032.

11) **"Pelvic Floor Repair"**[260]

[256] ETH.MESH.PM.000007, created 3-8-2006
[257] ETH.MESH.PM.000032, created 4-3-2007
[258] ETH.MESH.00419571-600
[259] ETH.MESH.PM.000052, created 4-3-2007
[260] ETH.MESH.PM.000019, created 7-23-2007

The video is approximately 100 minutes (1 hour, 20 minutes) and depicts an unedited total Prolift procedure with uterine conservation. The video is not formally narrated (unscripted); comments from the surgeon describe the procedure as it is performed. The primary surgeon is Douglas Van Drie, M.D.

An Ethicon disclaimer at the beginning of the video states that the video is not intended to be used as a procedure training guide. However, the setting in the operating room with observers and with Dr. Dennis Miller (an Ethicon preceptor for the Prolift procedures) implies that this is a training session.

General Comments on the Surgical Videos[261]

Safety

- All of the surgical videos depict primary prolapse procedures. Blunt dissection in the vesicovaginal and rectovaginal spaces is frequently described and depicted, although the technique of blunt dissection increases the risk of bladder, ureteral, and rectal injury, particularly in women who have had previous pelvic surgery for prolapse or incontinence.
- The documents (the original and revised Prolift IFUs, and the Prolift surgical technique document) and surgical videos do not consistently emphasize techniques to minimize the occurrence of surgical complications or to minimize the negative impact of surgical complications should they occur.
    - None of the documents and none of the surgical videos describe mesh contraction, the expected degree of mesh contraction, or how to account for mesh contraction in the anterior and posterior Prolift procedures.
    - In theory, the risk of vaginal mesh exposure is reduced by placing the mesh implant under the full thickness of the vagina. Hydrodissection is a technique using fluid infiltration to more easily identify and incise the full thickness of the vagina, and to more easily enter and dissect the vesicovaginal and rectovaginal spaces. In the Prolift surgical technique document, hydrodissection (not named as such) is listed as optional and incorrectly describes the technique as “infiltration of the vaginal wall” rather than deep to the vaginal wall. Only 1 of the 17 surgical videos provides complete information as to the exact type and amount of fluid used for hydrodissection, and how to assess whether the fluid has been injected into the correct space.
    - Despite the fact that full-thickness vaginal incisions and dissection in the vesicovaginal and rectovaginal spaces may be unfamiliar techniques for surgeons trained and experienced in traditional vaginal prolapse surgery, none of the documents and none of the videos specify techniques to protect the adjacent organs from injury during these steps of the anterior and posterior Prolift procedures.
    - Only approximately one-third of the videos depicted techniques to protect the adjacent organs during passage of the cannula-equipped guides, in agreement with the Prolift surgical technique document.

[261] Note: Although some of the surgical videos depict total Prolift procedures, my comments are organized by anterior and posterior Prolift procedures.

- None of the surgical videos adequately describe or depict the location of vital neurovascular structures and specific techniques for avoiding injury to those structures.
- The need for and appropriate timing of cystoscopy to detect and manage bladder and ureteral injury is not specified in any of the documents and is not depicted in 8 of the 9 videos of the anterior Prolift procedure.
- The need for and appropriate timing of rectal examination to detect and manage rectal injury is not specified in any of the documents and is not depicted in 6 of the 8 videos of the posterior Prolift procedure.

Prolapse Repair Techniques

- None of the documents and none of the videos describe or depict in any way how to objectively ensure standardized tension-free placement of the anterior and posterior segments of the Prolift mesh implant.
- When the Prolift procedure is performed with uterine conservation, the surgical videos describe and depict attachment of the mesh to the cervix, in contrast to the Prolift surgical technique document that describes attachment of the mesh to the uterus 2 cm above the cervix.
- None of the documents and only 1 of the 17 videos describes or depicts how to determine whether it is necessary to reduce the dimensions of the Prolift mesh implant, or how to determine by what amount the dimensions of the Prolift mesh implant should be reduced, based on different patient characteristics, or other factors.
- Although the Prolift surgical technique document recommends against suture fixation of the mesh implant to the vagina, 6 of the 17 videos describe and depict suture fixation of the mesh implant to the vagina, which has been described as a risk factor for vaginal mesh exposure.
- The intent of the anterior Prolift procedure is to provide support of the anterior vagina by mesh arm placement in relation to the arcus tendineus fascia pelvis (ATFP) and the ischial spine.
    - Only 2 of the 9 videos describe placement of the superficial anterior cannula-equipped guide at a specific distance relative to the ATFP, in agreement with the Prolift surgical technique document.
    - Only 3 of the 9 videos describe placement of the deep superficial anterior cannula-equipped guide at a specific distance relative to the ischial spine, in agreement with the Prolift surgical technique document.
    - Only 1 of the 9 videos describe placement of the body of the anterior mesh implant in lateral contact with the ATFP, in agreement with the Prolift surgical technique document.
    - Placement of the skin incisions for the superficial anterior cannula-equipped guides is described variably, either based on the level of the urethra or based on palpation of the bony landmarks, in contrast to the Prolift surgical technique document that assumes that the anteromedial edge of the obturator foramen and the level of the urethral meatus will be in the same horizontal plane in all patients. This inconsistency means that the entry points for the anterior Prolift trocars will differ markedly, affecting the entire placement of the anterior Prolift mesh implant.
- The intent of the posterior Prolift procedure is to provide support of the posterior vagina by mesh arm placement through the sacrospinous ligament in relation to the ischial spine.

- Five of the 8 videos do not describe or depict passage of the posterior cannula-equipped guide through the sacrospinous ligament at a specific distance in relation to the ischial spine.
- The remaining 3 of the 8 videos describe passage of the posterior cannula-equipped guide through the sacrospinous ligament at different distances in relation to the ischial spine, in contradiction to the 3-4 cm distance recommended in the Prolift surgical technique document. The different distances include 2 cm, 2.5-3 cm, and 1 or 2 fingerbreadths.
- None of the 8 videos describes placement of the body of the posterior mesh implant in lateral contact with the levator ani muscles, as stated in the Prolift surgical technique document.

Specific Comments on the Surgical Videos

Anterior Prolift Procedure

The anterior Prolift procedure is depicted using stylized anatomical images in the Anterior Repair segment of ETH.MESH.PM.000001. The anterior Prolift procedure is depicted surgically in 8 videos, including:

1. ETH.MESH.PM.000001 as part of a total Prolift procedure with uterine conservation (narrated by Dr. Rogers);
2. ETH.MESH.PM.000001 as part of a total Prolift procedure with vaginal hysterectomy and TVT-O (narrated by Dr. Rogers);
3. ETH.MESH.PM.000058 as part of a total Prolift procedure for posthysterectomy vaginal vault prolapse (not formally narrated by Dr. Lucente);
4. ETH.MESH.PM.000057 with laparoscopic visualization (narrated by Dr. Raders);
5. ETH.MESH.PM.000032 (narrated by Dr. Lucente);
6. ETH.MESH.PM.000032 as part of a total Prolift procedure with uterine conservation (narrated by Dr. Sepulveda);
7. ETH.MESH.PM.000032 as part of a total Prolift procedure for posthysterectomy vaginal vault prolapse (narrated by Dr. Sepulveda); and
8. ETH.MESH.PM.000019 as part of a total Prolift procedure with uterine conservation (not formally narrated by Dr. van Drie).

In summary, the 8 anterior Prolift procedures are performed:

- as part of a total Prolift procedure with uterine conservation in 3 videos;[262]
- alone in 2 videos;[263]
- as part of a total Prolift procedure for posthysterectomy vaginal vault prolapse in 2 videos;[264] and
- as a part of total Prolift procedure with vaginal hysterectomy in 1 video.[265]

[262] ETH.MESH.PM.000001 total Prolift with uterine conservation, ETH.MESH.PM.000032 total Prolift with uterine conservation, and ETH.MESH.PM.000019
[263] ETH.MESH.PM.000057 and ETH.MESH.PM.000032 anterior Prolift
[264] ETH.MESH.PM.000058 and ETH.MESH.PM.000032 total Prolift for posthysterectomy vaginal vault prolapse
[265] ETH.MESH.PM.000001 total Prolift with vaginal hysterectomy

Surgical steps of the anterior Prolift procedure are listed as follows:

1. Hydrodissection
2. Full-thickness anterior vaginal incision and dissection of the vesicovaginal space
3. Bladder plication
4. Anterior fixation of the anterior mesh implant to the uterus
5. Placement of the skin incision for the superficial anterior cannula-equipped guide
6. Placement of the superficial anterior cannula-equipped guide
7. Placement of the deep anterior cannula-equipped guide
8. Protecting the bladder and ureters from injury
   Anterior vaginal dissection
   Placement of superficial anterior cannula-equipped guides
   Placement of deep anterior cannula-equipped guides
9. Cystoscopy
10. Suture fixation of anterior mesh
11. Anterior mesh placement
12. Anterior mesh trimming
13. Adjustment of anterior mesh position and tension

1. Hydrodissection

- Neither the original nor the revised Prolift IFU even mention hydrodissection as an important step in the Prolift procedure.
- The Prolift surgical technique document does not name hydrodissection as such. Infiltration is listed as an optional step. The Prolift surgical technique document misstates correct placement of the solution, describing "infiltration of the vaginal wall" rather than infiltration deep to the vaginal wall to enter and expand the vesicovaginal space. The Prolift surgical technique document fails to provide specific information as to the type and amount of solution used, and how to assess whether the solution has been injected into the correct (vesicovaginal) space.
- Although all but 1 of the videos[266] describe hydrodissection, only 1 video[267] provides complete information as to the exact type and amount of solution to use, and how to assess whether the solution has been injected into the correct (vesicovaginal) space.
- Only 2 other videos[268] provide information about how to assess whether the solution has been injected into the correct (vesicovaginal) space.

2. Full-thickness anterior vaginal incision and dissection of the vesicovaginal space

- Despite the fact that full-thickness vaginal incision and dissection in the vesicovaginal space are generally unfamiliar techniques for surgeons trained and experienced in traditional vaginal prolapse surgery, neither the original nor the revised Prolift IFU identifies the importance of the full-thickness anterior vaginal incision or dissection in the vesicovaginal space in the anterior Prolift procedure; provides any information about how to ensure that the anterior vaginal incision is full-thickness; or provides any information

[266] ETH.MESH.PM.000001 Anterior Repair segment
[267] ETH.MESH.PM.000032 anterior Prolift
[268] ETH.MESH.PM.000057 and ETH.MESH.PM.000019

about the risk of bladder and ureteral injury and how to minimize that risk during the full-thickness anterior vaginal incision and dissection in the vesicovaginal space.

- Despite the fact that full-thickness vaginal incision and dissection in the vesicovaginal space are unfamiliar techniques for surgeons trained and experienced in traditional vaginal prolapse surgery, the Prolift surgical technique document does not provide any information about how to ensure that the anterior vaginal incision is full-thickness and does not provide any information about the risk of bladder and ureteral injury and how to minimize that risk during the full-thickness anterior vaginal incision and dissection in the vesicovaginal space.
- Two of the 9 videos[269] do not describe full-thickness anterior vaginal incisions.
- Two of the 9 videos[270] incorrectly describe the layers of the vagina in making the anterior vaginal incision.
- Only 1 of the 9 videos[271] describes and depicts how to identify that dissection is being performed in the correct (vesicovaginal) space.
- Only 1 of the 9 videos[272] mentions the risk of bladder injury during anterior vaginal incision and dissection in the vesicovaginal space; however, no specific information is provided about how to minimize the risk of bladder injury.
- None of the videos mention the risk of ureteral injury and how to minimize the risk of ureteral injury during anterior vaginal incision and dissection in the vesicovaginal space.

3. Bladder plication

- Neither the original and revised Prolift IFUs nor any of the videos state when bladder plication should or should not be performed, how it should be performed, and with what type of suture or stitches.
- The Prolift surgical technique document does not describe or depict bladder plication, as to deciding when it should or should not be performed, how it should be performed, and with what type of suture or stitches.

4. Anterior fixation of the anterior mesh implant to the uterus

- Neither the original nor the revised Prolift IFU describes fixation of the anterior mesh implant to the uterus.
- None of the documents (the original Prolift IFU, the revised Prolift IFU, and the Prolift surgical technique document) or videos describe mesh contraction, the expected degree of mesh contraction, and how to account for mesh contraction in the anterior Prolift procedure, relative to anterior fixation of the mesh implant to the uterus.
- The Prolift surgical technique document describes attachment of posterior part of the anterior segment of the mesh implant to the uterus 2 cm above the cervix with a Prolene (permanent) suture. The Prolift surgical technique document provides no information as to exactly when or how the anterior mesh implant is attached to the uterine stitch.

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[269] ETH.MESH.PM.000001 Anterior Repair segment and ETH.MESH.PM.000001 total Prolift with uterine conservation

[270] ETH.MESH.PM.000001 total Prolift with uterine conservation and ETH.MESH.PM.000032 total Prolift with uterine conservation

[271] ETH.MESH.PM.000032 anterior Prolift

[272] ETH.MESH.PM.000001 total Prolift with vaginal hysterectomy

- Three of the 9 videos refer to procedures where hysterectomy has been performed previously[273] or concomitantly;[274] therefore, this step does not apply.
- The Anterior Repair segment of ETH.MESH.PM.000001 does not describe or depict anterior mesh fixation to the uterus.
- The remaining 5 of 9 videos describe attachment of a permanent suture to the cervix (sometimes described as the pericervical ring), rather than to the uterus 2 cm above the cervix. Two of the 5 videos[275] do not name the suture or gauge used; the other 3 videos use different permanent sutures.[276]

5. Placement of the skin incisions for the superficial anterior cannula-equipped guides

- Neither the original nor revised Prolift IFUs provide any information regarding placement of the skin incisions (one on each side) for the superficial anterior cannula-equipped guides.
- The Prolift surgical technique document describes the placement of the skin incisions for the superficial anterior cannula-equipped guides (one on each side), assuming that the anteromedial edge of the obturator foramen and the level of the urethral meatus will be in the same horizontal plane in all patients.
- Four of the 9 videos[277] mark the placement of the skin incisions for the superficial anterior cannula-equipped guides based only on palpation of the bony landmarks, without regard to the level of the urethra.
- Three of the 9 videos[278] mark the placement of the skin incisions for the superficial anterior cannula-equipped guides based only on the level of the urethra without palpation of the bony landmarks.
- One of the 9 videos[279] marks the placement of the skin incisions for the superficial anterior cannula-equipped guides first based on the level of the urethra, and then changed based on palpation of the bony landmarks.
- One of the 9 videos[280] marks the placement of the skin incisions for the superficial anterior cannula-equipped guides based on palpation of the tendon of the adductor longus muscle.

6. Placement of the superficial anterior cannula-equipped guides

- Neither the original nor the revised Prolift IFU provides any information about placement of the superficial anterior cannula-equipped guides.
- The Prolift surgical technique document does not provide any information as to avoiding contact of the superficial anterior cannula-equipped guides with the bony edge of the

[273] ETH.MESH.PM.000058 and ETH.MESH.PM.000032 total Prolift for posthysterectomy vaginal vault prolapse
[274] ETH.MESH.PM.000001 total Prolift with vaginal hysterectomy
[275] ETH.MESH.PM.000001 total Prolift with uterine conservation and ETH.MESH.PM.000057
[276] ETH.MESH.PM.000032 anterior Prolift, Prolene of unstated gauge; ETH.MESH.PM.000032 total Prolift with uterine conservation, 3-0 Prolene; and ETH.MESH.PM.000019, 0 Novafil
[277] ETH.MESH.PM.000058, ETH.MESH.PM.000057, ETH.MESH.PM.000032 anterior Prolift, and ETH.MESH.PM.000032 total Prolift with uterine conservation
[278] ETH.MESH.PM.000001 Anterior Repair segment, ETH.MESH.PM.000001 total Prolift with uterine conservation, and ETH.MESH.PM.000001 total Prolift after vaginal hysterectomy
[279] ETH.MESH.PM.000032 total Prolift for posthysterectomy vaginal vault prolapse
[280] ETH.MESH.PM.000019

obturator foramen to avoid damage to the anterior branch of the obturator blood vessels, or how to correct placement if contact with the bony edge of the obturator foramen does occur.

- Only 2 of the 9 videos[281] state the location of placement of the superficial anterior cannula-equipped guide at a specific distance relative to the pubic arch or the arcus tendineus fasciae pelvis, in agreement with the Prolift surgical technique document.
- Although all of the videos depict the passage of the superficial anterior cannula-equipped guide, since guide passage is a blind technique, it is not possible to identify where its passage occurs relative to the pubic arch or the arcus tendineus fasciae pelvis, except in the video using stylized pelvic anatomy images[282] and in the video using laparoscopic visualization.[283]
- Two of the 9 videos[284] misstate the anatomical structures through which the superficial anterior cannula-equipped guides pass, by omitting passage through the obturator internus muscle after penetration of the obturator membrane.
- Only 2 of the 9 videos[285] provide information as to avoiding contact of the superficial anterior cannula-equipped guides with the bony edge of the obturator foramen to avoid damage to the anterior branches of the obturator blood vessels.
- None of the videos describes how to correct placement of the superficial anterior cannula-equipped guides if contact with the bony edge of the obturator foramen does occur.

7. Placement of the deep anterior cannula-equipped guides

- Neither the original nor the revised Prolift IFU provides any information about placement of the deep anterior cannula-equipped guides.
- The Prolift surgical technique document does not provide any information as to avoiding contact of the deep anterior cannula-equipped guides with the bony edge of the obturator foramen to avoid damage to the anterior branch of the obturator blood vessels, or how to correct placement if contact with the bony edge of the obturator foramen does occur.
- The Prolift surgical technique document and all of the videos provide no information about risk of injury to the pudendal nerve and blood vessels, and how to minimize that risk during placement of the deep anterior cannula-equipped guides near the ischial spine.
- One of the 9 videos[286] does not describe or depict placement of the deep anterior cannula-equipped guides.
- Only 3 of the 8 remaining videos[287] state the location of placement of the deep anterior cannula-equipped guides at a specific distance relative to the pubic arch or the arcus tendineus fascia pelvis, in agreement with the Prolift surgical technical document.

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[281] ETH.MESH.PM.000001 Anterior Repair segment and ETH.MESH.PM.000001 total Prolift with uterine conservation
[282] ETH.MESH.PM.000001 Anterior Repair segment
[283] ETH.MESH.PM.000057
[284] ETH.MESH.PM.000001 total Prolift with uterine conservation and ETH.MESH.PM.000057
[285] ETH.MESH.PM.000001 Anterior Repair segment and ETH.MESH.PM.000032 total Prolift for posthysterectomy vaginal vault prolapse
[286] ETH.MESH.PM.000058
[287] ETH.MESH.PM.000001 total Prolift with uterine conservation, ETH.MESH.PM.000032 total Prolift with uterine conservation, and ETH.MESH.PM.000032 total Prolift for posthysterectomy vaginal vault prolapse

- Two of the 8 remaining videos[288] do not describe passage of the deep anterior cannula-equipped guides at a specific distance relative to the ischial spine.
- Three of the 8 remaining videos[289] misstate the proper placement of the deep anterior cannula-equipped guides by describing placement at the ischial spine, rather than 1 cm from the ischial spine. This placement increases the risk of injury to the pudendal nerve and blood vessels as they pass behind the ischial spine.
- Although 8 of the 9 videos depict passage of the deep anterior cannula-equipped guides, since guide passage is a blind technique, it is not possible to identify where its passage occurs relative to the ischial spine, except in the video using stylized pelvic anatomy images[290] and in the video using laparoscopic visualization.[291]
- One of the 9 videos[292] misstates the anatomical structures through which the deep anterior cannula-equipped guides pass, by stating that the guides pass behind the levator plate.
- Only 1 of the 9 videos[293] provides information as to avoiding contact of the deep anterior cannula-equipped guides with the bony edge of the obturator foramen to avoid damage to the anterior branches of the obturator blood vessels, and how to correct placement of the deep anterior cannula-equipped guides if contact with the bony edge of the obturator foramen does occur.

8. Protecting the bladder and ureters from injury during anterior vaginal dissection and placement of the 4 anterior cannula-equipped guides

Anterior vaginal dissection

- Protecting the bladder and ureters from injury during anterior vaginal dissection is not mentioned in any of the documents (the original and revised Prolift IFUs, and the Prolift surgical technique document) and in 8 of the 9 videos.
- In the only 1 of the 9 videos[294] to mention the risk of bladder (but not ureteral) injury during anterior vaginal dissection, no specific information is provided as to how to minimize the risk of bladder and ureteral injury during anterior vaginal dissection.

Protecting the bladder and ureters from injury during placement of the 2 superficial anterior cannula-equipped guides

Only 1 of the 9 videos[295] describes protecting the bladder during passage of the 2 superficial anterior cannula-equipped guides, in agreement with the Prolift surgical technique document.

Protecting the bladder and ureters from injury during placement of the 2 deep anterior cannula-equipped guides

[288] ETH.MESH.PM.000001 Anterior Repair segment and ETH.MESH.PM.000001 total Prolift with vaginal hysterectomy
[289] ETH.MESH.PM.000057, ETH.MESH.PM.000032 anterior Prolift, and ETH.MESH.PM.000019
[290] ETH.MESH.PM.000001 Anterior Repair segment
[291] ETH.MESH.PM.000057
[292] ETH.MESH.PM.000019
[293] ETH.MESH.PM.000019
[294] ETH.MESH.PM.000001 total Prolift with vaginal hysterectomy
[295] ETH.MESH.PM.000032 total Prolift with uterine conservation

Only 3 of the 9 videos[296] describe protecting the bladder during passage of the 2 deep anterior cannula-equipped guides, in agreement with the Prolift surgical technique document.

9. Cystoscopy

- The appropriate timing of cystoscopy during the anterior Prolift procedure is after cannula placement and before mesh placement.
- The original Prolift IFU fails to indicate the need for and appropriate timing of cystoscopy to detect and manage bladder and ureteral injury.
- The revised Prolift IFU states that cystoscopy may be performed, but it fails to indicate the appropriate timing of cystoscopy.
- The Prolift surgical technique document does not mention cystoscopy at all, even after the Prolift IFU was revised to include a statement about cystoscopy.
- Seven of the 9 videos[297] do not mention cystoscopy at all.
- One of the 9 videos[298] describes and depicts cystoscopy at the appropriate time to detect and manage bladder and ureteral injury.
- One of the 9 videos[299] describes and depicts cystoscopy at the appropriate time only to detect and manage bladder injury, not ureteral injury.

10. Suture fixation of anterior mesh

- None of the documents (original and revised Prolift IFUs, the Prolift surgical technique document) and none of the videos describe mesh contraction, the expected degree of mesh contraction, and how to account for mesh contraction in the anterior Prolift procedure, relative to suture fixation of the anterior mesh.
- The Prolift surgical technique document describes optional suture fixation at the pubic insertions of the puborectalis muscles and additional optional suture fixations. The Prolift surgical technique document does not describe how to determine whether it is necessary to employ suture fixation of the anterior mesh implant, nor does it describe the type of suture and where to place suture fixation on the anterior mesh implant.
- None of the 9 videos describe or depict suture fixation of the anterior mesh implant to the puborectalis muscles, as suggested in the Prolift surgical technique document.
- None of the 9 videos describe how to determine whether it is necessary to employ suture fixation of the anterior mesh implant.
- Five of the 9 videos[300] do not describe or depict suture fixation of the anterior mesh implant to any location.

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[296] ETH.MESH.PM.000001 total Prolift with uterine conservation, ETH.MESH.PM.000001 total Prolift with vaginal hysterectomy, and ETH.MESH.PM.000032 total Prolift for posthysterectomy vaginal vault prolapse

[297] ETH.MESH.PM.000001, Anterior Repair segment; ETH.MESH.PM.000001, total Prolift with uterine conservation; ETH.MESH.PM.000001 total Prolift with vaginal hysterectomy; ETH.MESH.PM.000058 total Prolift for posthysterectomy vaginal vault prolapse; ETH.MESH.PM.000057, anterior Prolift with laparoscopic visualization; ETH.MESH.PM.000032 anterior Prolift; and ETH.MESH.PM.000032 total Prolift for posthysterectomy vaginal vault prolapse

[298] ETH.MESH.PM.000032, total Prolift with uterine conservation

[299] ETH.MESH.PM.000019

- Although the Prolift surgical technique document recommends against suture fixation of the mesh implant to the vagina,[301] 4 of the 9 videos[302] describe and depict absorbable suture fixation of the mesh implant to the vagina. Three videos[303] describe suture fixation of the anterior mesh implant to the urethrovesical junction, and 1 video describes suture fixation of the anterior mesh implant to the vaginal apex.[304]

11. Anterior mesh placement

- None of the documents (original and revised Prolift IFUs, the Prolift surgical technique document) and none of the 9 videos describe mesh contraction, the expected degree of mesh contraction, and how to account for mesh contraction in the anterior Prolift procedure, relative to anterior mesh placement in a standardized tension-free manner.
- None of the documents (original and revised Prolift IFUs, the Prolift surgical technique document) and none of the videos describe or depict in any way how to ensure standardized tension-free placement of the anterior segment of the Prolift mesh implant.
- Only 1 of the 9 videos[305] describes anterior mesh placement relative to the arcus tendineus fasciae pelvis (ATFP), as stated in the Prolift surgical technique document.
- Since the ATFP cannot be visualized during the anterior Prolift procedure, none of the videos depict visual verification of lateral contact of the anterior segment of the Prolift mesh implant with the ATFP.
- None of the videos describe or depict in any way how to ensure or carefully verify lateral contact of the anterior mesh implant with the ATFP.
- Only 2 of the 9 videos[306] described pulling the anterior cannulas back to the point where their distal ends are flush with the pelvic sidewall to bring the body of the mesh implant to the pelvic sidewall.

12. Anterior mesh trimming

- None of the documents (original and revised Prolift IFUs, the Prolift surgical technique document) and none of the videos describe mesh contraction, the expected degree of mesh contraction, and how to account for mesh contraction in the anterior Prolift procedure, relative to anterior mesh trimming to reduce the dimensions of the anterior Prolift mesh implant.
- None of the documents (original and revised Prolift IFUs, the Prolift surgical technique document) and none of the videos describe or depict how to determine whether it is necessary to reduce the dimensions of the anterior mesh implant, or how to determine by

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[300] ETH.MESH.PM.000001 Anterior repair segment, ETH.MESH.PM.00001 total Prolift with uterine conservation, ETH.MESH.PM.00001 total Prolift with vaginal hysterectomy, ETH.MESH.PM.000058, and ETH.MESH.PM.000032 total Prolift with uterine conservation

[301] ETH.MESH.00419572, page 2: "It is recommended to avoid … fixation of the vagina to the implant."

[302] ETH.MESH.PM.000057, ETH.MESH.PM.000032 anterior Prolift, ETH.MESH.PM.000032 total Prolift for posthysterectomy vaginal vault prolapse, and ETH.MESH.PM.000019

[303] ETH.MESH.PM.000057, ETH.MESH.PM.000032 anterior Prolift, and ETH.MESH.PM.000019

[304] ETH.MESH.PM.000032 total Prolift for posthysterectomy vaginal vault prolapse

[305] ETH.MESH.PM.000001, total Prolift with uterine conservation

[306] ETH.MESH.PM.000057 and ETH.MESH.PM.000032 anterior Prolift

what amount the dimensions of the anterior mesh implant should be reduced, based on different patient characteristics.

- Only 1 of the 9 videos[307] describes and depicts anterior mesh trimming. Although the video states that the mesh trimming can be custom made for different patients, the video does not describe or depict how to determine by what amount the dimensions of the anterior mesh implant should be reduced, based on different patient characteristics.

13. Adjustment of anterior mesh position and tension

- Neither the original nor revised Prolift IFUs provide any information regarding the adjustment of the anterior mesh position and tension. In addition, neither the original nor the revised Prolift IFUs describe mesh contraction, the expected degree of mesh contraction, and how to account for mesh contraction in the anterior Prolift procedure, relative to adjustment of the anterior mesh implant position and tension.
- The Prolift surgical technique document states that fine adjustment of the anterior mesh position and tension may be performed after closure of the vaginal incision. However, the Prolift surgical technique document does not describe mesh contraction, the expected degree of mesh contraction, and how to account for mesh contraction in the anterior Prolift procedure, relative to adjustment of the anterior mesh implant position and tension; and does not describe or depict how to assess or adjust the anterior mesh implant in a standardized, tension-free manner.
- None of the 9 videos describe mesh contraction, the expected degree of mesh contraction, and how to account for mesh contraction in the anterior Prolift procedure, relative to adjustment of the anterior mesh implant position and tension.
- None of the 9 videos describe or depict how to adjust the anterior mesh implant in a standardized, tension-free manner.
- Four of the 9 videos[308] describe manually replacing the vagina in the pelvis and exerting vaginal pressure while observing the mesh arms retract through the cannula openings. Of these 4 videos, 2 videos provide no description of the length of mesh arm retraction;[309] 1 video states mesh arm retraction of 3 cm;[310] and the remaining video states mesh arm retraction of 1-1.5 cm.[311]
- One of the 9 videos[312] describes manually replacing the vagina in the pelvis.
- Three of the 9 videos[313] provide no information about adjusting the anterior mesh position and tension.

<u>Posterior Prolift Procedure</u>

[307] ETH.MESH.PM.000032 anterior Prolift
[308] ETH.MESH.PM.000032 anterior Prolift, ETH.MESH.PM.000032 total Prolift with uterine conservation, ETH.MESH.PM.000032 total Prolift for posthysterectomy vaginal vault prolapse, and ETH.MESH.PM.000019
[309] ETH.MESH.PM.000032 total Prolift with uterine conservation, ETH.MESH.PM.000032 total Prolift for posthysterectomy vaginal vault prolapse
[310] ETH.MESH.PM.000032 anterior Prolift
[311] ETH.MESH.PM.000019
[312] ETH.MESH.PM.000001 total Prolift with vaginal hysterectomy
[313] ETH.MESH.PM.000001 Anterior Repair segment, ETH.MESH.PM.000001 total Prolift with uterine conservation, and ETH.MESH.PM.000058 posthysterectomy vaginal vault prolapse

The posterior Prolift procedure is depicted using stylized anatomical images in the Posterior Repair segment of ETH.MESH.PM.000001. The posterior Prolift procedure is depicted surgically in 7 videos, including:

1. ETH.MESH.PM.000001 as part of a total Prolift procedure with uterine conservation (narrated by Dr. Rogers);
2. ETH.MESH.PM.000001 as part of a total Prolift procedure with vaginal hysterectomy and TVT-O (narrated by Dr. Rogers);
3. ETH.MESH.PM.000058 as part of a total Prolift procedure for posthysterectomy vaginal vault prolapse (performed but not narrated by Dr. Lucente);
4. ETH.MESH.PM.000032 (narrated by Dr. Lucente);
5. ETH.MESH.PM.000032 as part of a total Prolift procedure with uterine conservation (narrated by Dr. Sepulveda);
6. ETH.MESH.PM.000032 as part of a total Prolift procedure for posthysterectomy vaginal vault prolapse (narrated by Dr. Sepulveda); and
7. ETH.MESH.PM.000019 as part of a total Prolift procedure with uterine conservation (performed but not formally narrated by Dr. van Drie).

In summary, the 7 posterior Prolift procedures are performed:

- as part of a total Prolift procedure with uterine conservation in 3 videos;[314]
- alone in 1 video;[315]
- as part of a total Prolift procedure for posthysterectomy vaginal vault prolapse in 2 videos;[316] and
- as a part of total Prolift procedure with vaginal hysterectomy in 1 video.[317]

Surgical steps of the posterior Prolift procedure are listed as follows:

1. Hydrodissection
2. Full-thickness posterior vaginal incision and dissection in the rectovaginal space
3. Rectal plication
4. Enterocele reduction
5. Posterior mesh fixation to the uterus
6. Placement of posterior skin incisions
7. Placement of posterior cannula-equipped guide in the sacrospinous ligament relative to the ischial spine
8. Protecting the rectum from injury
   Posterior vaginal dissection
   Posterior cannula-equipped guide placement
9. Posterior mesh placement
10. Posterior mesh trimming
11. Adjustment of posterior mesh position and tension

[314] ETH.MESH.PM.000001 total Prolift with uterine conservation, ETH.MESH.PM.000032 total Prolift with uterine conservation, and ETH.MESH.PM.000019
[315] ETH.MESH.PM.000032 posterior Prolift
[316] ETH.MESH.PM.000058 and ETH.MESH.PM.000032 total Prolift for posthysterectomy vaginal vault prolapse
[317] ETH.MESH.PM.000001 total Prolift with vaginal hysterectomy

12. Suture fixation of posterior mesh
13. Rectal examination

1. Hydrodissection

- Neither the original nor the revised Prolift IFU identify hydrodissection as an important step in the Prolift procedure.
- The Prolift surgical technique document does not adequately identify hydrodissection as such. Infiltration is listed as an optional step. The Prolift surgical technique document misstates correct placement of the solution, describing "infiltration of the vaginal wall" rather than infiltration deep to the vaginal wall to expand the rectovaginal space. The Prolift surgical technique document fails to provide specific information as to the type and amount of solution used, and how to assess whether the solution has been injected into the correct (rectovaginal) space.
- Two of the 8 videos[318] do not describe hydrodissection.
- None of the remaining 6 videos provides complete information as to the exact type and amount of solution to use for hydrodissection.
- None of the remaining 6 videos describe or depict how to assess whether the solution has been injected into the correct (rectovaginal) space.

2. Full-thickness posterior vaginal incision and dissection in the rectovaginal space

- Despite the fact that full-thickness posterior vaginal incision and dissection in the rectovaginal space are largely unfamiliar techniques for surgeons trained and experienced in traditional vaginal prolapse surgery, neither the original nor the revised Prolift IFU identifies the importance of the full-thickness posterior vaginal incision or dissection in the rectovaginal space in the Prolift procedure; provides any information about how to ensure that the posterior vaginal incision is full-thickness; or provides any information about the risk of rectal injury and how to minimize that risk during the full-thickness posterior vaginal incision and dissection in the rectovaginal space.
- Despite the fact that full-thickness posterior vaginal incision and dissection in the rectovaginal space are largely unfamiliar techniques for surgeons trained and experienced in traditional vaginal prolapse surgery, the Prolift surgical technique document does not provide any information about how to ensure that the posterior vaginal incision is full-thickness and does not provide any specific information about the risk of rectal injury and how to minimize that risk during the full-thickness posterior vaginal incision and dissection in the rectovaginal space.
- Two of the 8 videos[319] incorrectly describe the layers of the vagina in making the posterior vaginal incision.
- None of the 8 videos describe or depict how to ensure that the posterior vaginal incision is full thickness.
- None of the 8 videos describe or depict how to identify that dissection is being performed in the correct (rectovaginal) space.

[318] ETH.MESH.PM.000001 Posterior Repair segment and ETH.MESH.PM.000058
[319] ETH.MESH.PM.000001 Posterior Repair segment and ETH.MESH.PM.000032 total Prolift with uterine conservation

- Only 1 of the 8 videos[320] describes a maneuver related to the risk of rectal injury during posterior vaginal incision.
- None of the videos describe or depict how to minimize the risk of rectal injury during dissection in the rectovaginal space.

3. Rectal plication

- Rectal plication is not mentioned in the original and revised Prolift IFUs and any of the 8 videos, as to deciding when it should or should not be performed, how it should be performed, and with what type of suture or stitches.
- The Prolift surgical technique document does not describe or depict rectal plication, as to deciding when it should or should not be performed, how it should be performed, and with what type of suture or stitches.

4. Enterocele reduction

- Enterocele reduction is not mentioned in the original and revised Prolift IFUs and 7 of the 8 videos, as to deciding when it should or should not be performed, how it should be performed, and with what type of suture or stitches.
- The Prolift surgical technique document does not describe or depict enterocele reduction, as to deciding when it should or should not be performed, how it should be performed, and with what type of suture or stitches.
- In the only 1 of the 8 videos[321] that mentions enterocele reduction, it does not describe or depict how it should be performed, and with what type of suture or stitches.

5. Posterior mesh fixation to the uterus

- Neither the original nor the revised Prolift IFU describes fixation of the posterior mesh implant to the uterus.
- None of the documents (the original Prolift IFU, the revised Prolift IFU, and the Prolift surgical technique document) and none of the videos describe mesh contraction, the expected degree of mesh contraction, and how to account for mesh contraction in the posterior Prolift procedure, relative to posterior fixation of the mesh implant to the uterus.
- The Prolift surgical technique document describes attachment of anterior part of the posterior segment of the mesh implant to the uterus 2 cm above the cervix with a Prolene [permanent] suture. The Prolift surgical technique document provides no information as to exactly when or how the posterior mesh implant is attached to the uterine stitch.
- Four of the 8 videos refer to procedures where hysterectomy has been performed previously[322] or concomitantly;[323] therefore, this step does not apply.
- The Posterior Repair segment of ETH.MESH.PM.000001 does not describe or depict posterior mesh fixation to the uterus.

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[320] ETH.MESH.PM.000019
[321] ETH.MESH.PM.000019
[322] ETH.MESH.PM.000058, ETH.MESH.PM.000032 posterior Prolift, and ETH.MESH.PM.000032 total Prolift for posthysterectomy vaginal vault prolapse
[323] ETH.MESH.PM.000001 total Prolift with vaginal hysterectomy

- The remaining 3 of the 8 videos describe attachment of a permanent suture to the cervix (sometimes described as the pericervical ring), rather than to the uterus 2 cm above the cervix. Two of the 3 videos[324] do not name the suture or gauge used; the remaining video uses permanent suture.[325]

6. Placement of posterior skin incisions

- Neither the original nor the revised Prolift IFU provide any information as to the correct placement of the posterior skin incisions.
- The Prolift surgical technique document describes the anus as the reference point for placing the posterior skin incisions.
- Four of the 8 videos describe different reference points for placing the posterior skin incisions, including the mid anal verge,[326] the anal sphincter,[327] the anal orifice,[328] and the rectum.[329]

7. Placement of posterior cannula-equipped guide in the sacrospinous ligament relative to the ischial spine

- Neither the original nor revised Prolift IFU provide any information about the placement of the posterior cannula-equipped guide in the sacrospinous ligament relative to the ischial spine in terms of effectiveness of providing apical vaginal support.
- Except for 1 video,[330] none of the documents (original and revised Prolift IFUs, Prolift surgical technique document) and none of the remaining 7 videos identify major nerves and vascular structures at risk of injury during passage of the posterior cannula-equipped guide.
- One of the 8 videos[331] does not depict placement of the posterior cannula-equipped guides at all.
- Four of the remaining 7 videos[332] do not describe or depict passage of the posterior cannula-equipped guide through the sacrospinous ligament at a specific distance in relation to the ischial spine.
- Each of the remaining 3 videos describe passage of the posterior cannula-equipped guide through the sacrospinous ligament at different points in relation to the ischial spine, in contradiction to the 3-4 cm distance recommended in the Prolift surgical technique document. One video[333] states the distance as 2 cm; one video[334] states the distance as 1 or 2 fingerbreadths, and one video[335] states the distance as 2.5-3 cm. These contradictions are

[324] ETH.MESH.PM.000001 total Prolift with uterine conservation and ETH.MESH.PM.000019
[325] ETH.MESH.PM.000032 total Prolift with uterine conservation, 3-0 Prolene
[326] ETH.MESH.PM.000032 posterior Prolift
[327] ETH.MESH.PM.000032 total Prolift with uterine conservation
[328] ETH.MESH.PM.000032 total Prolift for posthysterectomy vaginal vault prolapse
[329] ETH.MESH.PM.000019
[330] ETH.MESH.PM.000001 Posterior Repair segment
[331] ETH.MESH.PM.000058
[332] ETH.MESH.PM.000001 total Prolift with uterine conservation, ETH.MESH.PM.000001 total Prolift with vaginal hysterectomy, ETH.MESH.PM.000032 total Prolift with uterine conservation, and ETH.MESH.PM.000032 total Prolift for posthysterectomy vaginal vault prolapse
[333] ETH.MESH.PM.000001 Posterior Repair segment
[334] ETH.MESH.PM.000032 posterior Prolift
[335] ETH.MESH.PM.000019

critically important because of the vital structures at risk for injury during placement of the posterior cannula-equipped guide through the sacrospinous ligament. Near the origin of the sacrospinous ligament and coccygeus muscle at the ischial spine, the pudendal nerve and blood vessels pass behind the ischial spine. Near the insertion of the sacrospinous ligament and coccygeus muscle at the lateral border of the coccyx and most caudad segment of the sacrum, the inferior gluteal nerve and blood vessels pass over the upper posterior edge of the sacrospinous ligament. The use of a standard distance, knowing that the distance would vary from patient to patient, was unreasonable.

- None of the 7 surgical videos depict the passage of the cannula-equipped guide through the sacrospinous ligament, although 2 videos[336] narrate this step as if it is visualized. Due to the depth of the sacrospinous ligament, none of the videos were able to depict this critically important step of the posterior Prolift procedure.

8. Protecting the rectum from injury

Protecting the rectum from injury during posterior vaginal dissection

- Specific techniques to protect the rectum from injury during posterior vaginal dissection are not mentioned in any of the documents (the original and revised Prolift IFUs, and the Prolift surgical technique document) and 7 of the 8 videos.
- Only 1 of the 8 videos[337] describes a technique to reduce the risk of rectal injury during posterior vaginal incision, but no specific information is provided as to how to minimize the risk of rectal injury during posterior vaginal dissection.

Protecting the rectum from injury during placement of the 2 posterior cannula-equipped guides

Although the Prolift surgical technique document recommends deflecting the rectum during passage of the 2 posterior cannula-equipped guides, only 3 of the 8 videos[338] mention performing this technique.

9. Posterior mesh placement

- None of the documents (original and revised Prolift IFUs, the Prolift surgical technique document) and none of the 8 videos describe mesh contraction, the expected degree of mesh contraction, and how to account for mesh contraction in the posterior Prolift procedure, relative to posterior mesh placement in a standardized tension-free manner.
- None of the documents (original and revised Prolift IFUs, the Prolift surgical technique document) and none of the 8 videos describe or depict in any way how to ensure or assess standardized tension-free placement of the posterior segment of the Prolift mesh implant.
- None of the 8 videos describes posterior mesh placement relative to the levator ani muscles, as stated in the Prolift surgical technique document.

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[336] ETH.MESH.PM.000001 total Prolift with uterine conservation and ETH.MESH.PM.000001 total Prolift with vaginal hysterectomy: Each video narrates that "The tip of [posterior] cannula-equipped guide is then seen passing through the sacrospinous ligament."

[337] ETH.MESH.PM.000019

[338] ETH.MESH.PM.000001 total Prolift with vaginal hysterectomy, ETH.MESH.PM.000058, and ETH.MESH.PM.000032 total Prolift with uterine conservation

- Since the levator ani muscles cannot be visualized during the posterior Prolift procedure, none of the videos depict visual verification of lateral contact of the posterior segment of the Prolift mesh implant with the levator ani muscles.
- Only 1 of the 8 videos[339] describes palpation of the posterior Prolift mesh implant in the rectovaginal space; however, this step is not depicted visually in the video.

10. Posterior mesh trimming

- None of the documents (original and revised Prolift IFUs, the Prolift surgical technique document) and none of the videos describe mesh contraction, the expected degree of mesh contraction, and how to account for mesh contraction in the posterior Prolift procedure, relative to posterior mesh trimming to reduce the dimensions of the posterior Prolift mesh implant.
- None of the documents (original and revised Prolift IFUs, the Prolift surgical technique document) and only 1 of the 8 videos[340] describes how to determine whether it is necessary to reduce the dimensions of the posterior mesh implant. That video describes how to determine by what amount the distal segment of the posterior mesh implant should be reduced, based on the patient's vaginal length with the cervix reduced.
- Six of the 8 videos[341] depict posterior mesh trimming. However, with the exception noted above, the remaining 5 videos do not describe or depict how to determine by what amount the dimensions of the anterior mesh implant should be reduced, based on different patient characteristics. The amount of posterior mesh trimming is either not stated,[342] stated vaguely,[343] or stated arbitrarily without regard to different patient characteristics.[344]

11. Adjustment of posterior mesh position and tension

- Neither the original nor revised Prolift IFUs provide any information regarding the adjustment of the posterior mesh position and tension. In addition, neither the original nor the revised Prolift IFUs describe mesh contraction, the expected degree of mesh contraction, and how to account for mesh contraction in the posterior mesh Prolift procedure, relative to adjustment of the posterior mesh implant position and tension.
- The Prolift surgical technique document states that fine adjustment of the posterior mesh position and tension may be performed after closure of the vaginal incision. However, the Prolift surgical technique document does not describe mesh contraction, the expected degree of mesh contraction, and how to account for mesh contraction in the posterior Prolift procedure, relative to adjustment of the posterior mesh implant position and tension; and does not describe or depict how to assess or adjust the posterior mesh implant in a standardized, tension-free manner.

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[339] ETH.MESH.PM.000001 total Prolift with uterine conservation
[340] ETH.MESH.PM.000019
[341] ETH.MESH.PM.000032 posterior Prolift
[342] ETH.MESH.PM.000058
[343] ETH.MESH.PM.000001 total Prolift with vaginal hysterectomy: "a little"; ETH.MESH.PM.000032 total Prolift with uterine conservation: "excess"
[344] ETH.MESH.PM.000001 total Prolift with uterine conservation: "1 cm"; ETH.MESH.PM.000032 posterior Prolift: "at the second blue line"

- None of the 8 videos describe mesh contraction, the expected degree of mesh contraction, and how to account for mesh contraction in the posterior Prolift procedure, relative to adjustment of the posterior mesh implant position and tension.
- None of the 8 videos describe or depict how to assess or adjust the posterior mesh implant in a standardized, tension-free manner.
- Four of the 8 videos[345] describe manually replacing the vagina in the pelvis and exerting vaginal pressure while observing the mesh arms retract through the cannula openings. Of these 4 videos, 2 videos provide no description of the length of mesh arm retraction;[346] 1 video states mesh arm retraction of 3 cm;[347] and the remaining video states mesh arm retraction of 1-1.5 cm.[348]
- Two of the 8 videos[349] describe manual palpation of the posterior vagina to position the posterior Prolift mesh implant.
- Two of the 8 videos[350] provide no information about adjusting the posterior mesh position and tension.
- All of the documents (original and revised Prolift IFUs and Prolift surgical technique document) and 4 of the 8 videos[351] fail to indicate the use of rectal palpation in adjusting the position and tension of the posterior Prolift mesh implant.
- Although 4 of the 8 videos[352] indicate the use of rectal palpation in adjusting the position and tension of the posterior Prolift mesh implant, none of the documents (original and revised Prolift IFUs and Prolift surgical technique document) and none of the videos describe or depict how to assess or adjust the posterior Prolift mesh implant via rectal palpation in a standardized, tension-free manner.

12. Suture fixation of posterior mesh

- None of the documents (original and revised Prolift IFUs, the Prolift surgical technique document) and none of the videos describe mesh contraction, the expected degree of mesh contraction, and how to account for mesh contraction in the posterior Prolift procedure, relative to suture fixation of the posterior mesh.
- The Prolift surgical technique document describes optional suture fixation at the levator ani muscles. The Prolift surgical technique document does not describe how to determine whether it is necessary to employ suture fixation of the posterior mesh implant, nor does it describe the type of suture and where to place suture fixation on the posterior mesh implant.

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[345] ETH.MESH.PM.000032 posterior Prolift, ETH.MESH.PM.000032 total Prolift with uterine conservation, ETH.MESH.PM.000032 total Prolift for posthysterectomy vaginal vault prolapse, and ETH.MESH.PM.000019

[346] ETH.MESH.PM.000032 total Prolift with uterine conservation, ETH.MESH.PM.000032 total Prolift for posthysterectomy vaginal vault prolapse

[347] ETH.MESH.PM.000032 posterior Prolift

[348] ETH.MESH.PM.000019

[349] ETH.MESH.PM.000001 total Prolift with uterine conservation and ETH.MESH.PM.000001 total Prolift with vaginal hysterectomy

[350] ETH.MESH.PM.000001 Posterior Repair segment and ETH.MESH.PM.000058

[351] ETH.MESH.PM.000001 Posterior Repair segment, ETH.MESH.PM.000001 total Prolift with uterine conservation, ETH.MESH.PM.000001 total Prolift with vaginal hysterectomy, and ETH.MESH.PM.000058

[352] ETH.MESH.PM.000032 posterior Prolift, ETH.MESH.PM.000032 total Prolift with uterine conservation, ETH.MESH.PM.000032 total Prolift for posthysterectomy vaginal vault prolapse, and ETH.MESH.PM.000019

- None of the 8 videos describe or depict suture fixation of the posterior mesh implant to the levator ani muscles, as suggested in the Prolift surgical technique document.
- None of the 8 videos describe how to determine whether it is necessary to employ suture fixation of the posterior mesh implant.
- Six of the 8 videos[353] do not describe or depict suture fixation of the posterior mesh implant to any location.
- Although the Prolift surgical technique document recommends against suture fixation of the mesh implant to the vagina,[354] 2 of the 8 videos[355] describe and depict absorbable suture fixation of the mesh implant to the perineal body.

13. Rectal examination to detect and manage rectal injury

- The appropriate timing of rectal examination to detect and manage rectal injury during the posterior Prolift procedure is after cannula placement and before mesh placement.
- The need for and appropriate timing of rectal examination to detect and manage rectal injury during the posterior Prolift procedure is not mentioned at all in the original Prolift IFU, the Prolift surgical technique document, and 4 of the 8 videos.[356]
- The revised Prolift IFU states that rectal examination should be performed, but it fails to indicate the appropriate timing.
- The Prolift surgical technique document does not mention rectal examination at all, even after the Prolift IFU was revised to include a statement about rectal examination.
- Two of the remaining 4 videos[357] depict inappropriate timing of rectal examination to detect and manage rectal injury during the posterior Prolift procedure.
- Only 2 of the 8 videos[358] depict rectal examination at the appropriate time to detect and manage rectal injury during the posterior Prolift procedure.

Ethicon Training Sessions[359]

[353] ETH.MESH.PM.000001 Posterior repair segment, ETH.MESH.PM.00001 total Prolift with uterine conservation, ETH.MESH.PM.00001 total Prolift with vaginal hysterectomy, ETH.MESH.PM.000058, ETH.MESH.PM.000032 total Prolift with uterine conservation, and ETH.MESH.PM.000032 total Prolift for posthysterectomy vaginal vault prolapse

[354] ETH.MESH.00419572, page 2: "It is recommended to avoid … fixation of the vagina to the implant."

[355] ETH.MESH.PM.000032 posterior Prolift and ETH.MESH.PM.000019

[356] ETH.MESH.PM.000001 Posterior Repair segment, ETH.MESH.PM.000058, ETH.MESH.PM.000032 posterior Prolift, and ETH.MESH.PM.000019

[357] ETH.MESH.PM.000001 total Prolift with uterine conservation and ETH.MESH.PM.000001 total Prolift with vaginal hysterectomy

[358] ETH.MESH.PM.000032 total Prolift with uterine conservation and ETH.MESH.PM.000032 total Prolift for posthysterectomy vaginal vault prolapse

[359] ETH-00933-00934

- Preceptorships — preceptee learns procedure via didactic presentation and observation of 3-4 surgeries at the preceptors hospital.
- Proctorships — preceptee learns the procedure via didactic presentation and preceptor "walks them through" the procedure at the preceptee's hospital.
- Cadaver lab — anatomic, cadaver training and didactic on the procedure and placement of the device.

Ethicon offered training sessions in the format of cadaver labs, proctorships, and preceptorships, accompanied by didactic lectures by physicians paid by Ethicon, using Ethicon copy reviewed training materials including professional education PowerPoint slide presentations.

The context of this training, particularly the copy-reviewed PowerPoint decks, was expected by surgeons to provide accurate information about the Prolift Systems, including the risks and benefits, both intrinsic and in comparison to the alternative procedures available. This information was expected by physician trainees to be fair and balanced. In vivid contrast to Ethicon's claim of providing physicians with fair and balanced information, as just one example, set out in the Prolift professional education strategy, Ethicon planned to collect and distribute information from the medical literature, "to support use of meshes and fight competition."[360] Further significant inaccuracies and inadequacies of these materials are described herein.

Inconsistent Criteria for Surgeon Selection for Prolift Training

Ethicon recognized that the Prolift required significant surgical skill to implant, and the Prolift product was only intended to be used by the most highly skilled surgeons. Despite these criteria, soon after Prolift's launch, many surgeons required re-training in the highly complex Prolift procedures.[361] Scott Jones confirmed that, "It's known that the Prolift can be – is a complex procedure and can have a steep learning curve."[362] There is also substantial documentation that Ethicon actually knew and intended that after the initial launch to highly skilled pelvic floor mesh surgeons, the Prolift would be marketed to lesser skilled physicians..[363] In a November 25, 2005 email, Axel Arnaud confirmed that he told European surgeon Professor Jakob Eberhard, who had numerous legitimate concerns about the safety of the Prolift, "that our device is designed to be safe even in the less skilled hands."[364] This contradicts testimony of others in Ethicon that the Prolift was designed to only be used in the most highly skilled hands. Since Ethicon had to approve a physician for training, and medical affairs intended less skilled surgeons to use the Prolift, Ethicon had to foresee that complications would occur in higher numbers than if only the most highly skilled surgeons used the Prolift.

The Ethicon documents establish that, despite the recognition that only the most highly skilled pelvic floor surgeons should be trained, Ethicon knew and intended that less skilled and less experienced surgeons would be trained in order to maximize sales of the Prolift. For example, Ethicon used professional education courses to convert non-mesh surgeons to using mesh for prolapse repair.[365] In fact, Ethicon encouraged inexperienced surgeons to use mesh in cases for

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[360] ETH.MESH.00129547, Prolift professional education strategy, November 2004: "A list of articles collected by HE&R [Health Economics & Reimbursement] to support use of meshes and fight competition."

[361] ETH-62214, p. 556: Email from Amy Vie, Professional education development manager, 5-17-2005 "… 16 of the 84 [number of surgeons trained as of May 3] have needed to be re-trained (19%) …

[362] Scott Jones dep., 71:17-20

[363] David Robinson dep., 376:14-24

[364] ETH.MESH.001133503.

[365] 9-21-04, ETH-60136-60137: email from Marianne Kaminski: "We have additional budget for Gynemesh PS 'market seeding' via PE [professional education] courses!!!!!"
10-7-04, ETH-60136: email from Giselle Bonet: "It is critical that we expand our user base of Gynemesh this year so that we can have a successful launch of our next generation pelvic floor product in Q1."

which mesh might not be indicated at all, including early-stage prolapse.[366] Beginning shortly after Prolift launch, Ethicon received complaints from proctors and others about surgeons with insufficient skill and knowledge attending the Prolift training sessions.[367] Despite vague assurances that changes were made to address these issues, year after year, Ethicon continued to received complaints of the same nature that clearly indicated surgeons of inappropriate skill and knowledge were being trained to perform the Prolift procedures, at least in part because Prolift sales representatives aggressively pushed surgeons into the training.[368] Even though Ethicon anticipated this situation,[369] Ethicon did nothing proactively or reactively to address the problems, and the complaints and concerns from proctors and others continued.[370] Scott Jones confirmed that the 2008 Pelvic Floor Business Plan provided that due to "market saturation of skilled pelvic organ prolapse experts," less skilled surgeons would be targeted for training.[371]

The significance of this issue cannot be overstated. Ethicon knew from the outset that surgical skill and knowledge would be outcome determinative, and that all surgeons would be expected to have higher complication rates earlier in their learning curves. Ethicon compromised patient safety by failing to ensure a high skill level for all trainees, and by failing to advise physicians and patients about the significance of surgeon skill and experience, and the steep learning curve that the Prolift procedure entailed.

3-24-05: ETH-60149: email from Greg Prine, Division Sales Manager: "One of our biggest challenges moving forward will be our ability to clearly communicate with our physicians how to use Gynemesh tension free in POP procedures. This will also help to ensure a healthy pipeline of targets for Prolift moving forward. This information should be helpful in shorten the learning curve with your physicians that are just starting to use mesh. We need to prepare our future Prolift users, today."

[366] ETH-60151, sent from Greg Prine, 3-24-2005, "tips regarding how to improve results when using mesh in POP cases": "Use Gynemesh in smaller repairs (grade 1 or 2) and begin to feel comfortable with using a synthetic."

[367] 12-10-2005, ETH-83193: email from Dennis Miller [proctor] to Eric Dastmalchian with feedback on preceptorships: "I think the 2006 cadaver lab attendee's are going to be less knowledgeable than the 2005 group. They already seem to be less aware of anatomy. The next round of Doctors attending cadaver lab are also going to include more surgeons who are somewhat less qualified and therefore need more direct one-on-one help. This is especially true if they plan on doing Prolift without O.R. experience. … Ideally we have one proctor per cadaver. I would rather have more doctors on a cadaver than have them sitting in front of a cadaver without a proctor. I thought a couple of those guys were going to poke somebody's eye out."

[368] 6-27-2006, ETH-83318, email from Tim Sweatt [District Manager] to Giselle Bonet: "Too often we send surgeons to training on Prolift who in reality should only use Gynemesh at this time, but they want to train and if we don't, our competition will train them. The reps push the envelope on training because they don't want to see a repeat of the obturator wars, where we were in a catch up position from launch. Our current labs don't really discuss Gynemesh, which is what most doctors should in fact be using at this point."

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[370] 8-10-09, ETH-49659: email form Aaron Kirkemo to Harel Gadot, Jonathan Meek, Scott Jones, Clifford Volpe, Lynn Hall, Peter Meier, David Robinson, Vincenza Zaddem, Piet Hinoul: "… The 'Tier 1' docs are very concerned that the 'Tier 2 and 3' docs lack the skill set to use the trocar/cannula system of Prolift. They felt that the lower tier docs both don't have the anatomic knowledge or the surgical skills to use these tools. Consequently they opt for the devices that allow them to more comfortably work in areas that they have at least a modicum of anatomic knowledge/comfort."

[371] Jones dep., 731:18-732:3; 733:15-734:22

VIII. The Lack of Adequate Clinical Study of the Prolift

The Prolift was an experimental POP treatment system launched based on speculation and hope that this system would offer better effectiveness than traditional vaginal prolapse repair. At the same time, Ethicon ignored significant evidence in the literature and their own experience with hernia mesh and Gynemesh PS mesh that would have led any reasonable person to expect the product to cause significant complications and risks.

Scott Jones acknowledged that one option available to Ethicon was to not make the Prolift commercially available until clinical trials could be conducted to establish that the Prolift product and procedure was safe and effective, but Ethicon chose to go directly to market.[372] The Prolift was not adequately studied before it was launched. Very telling is the history of the Prolift Clinical Expert Report, discussed above.

ACOG Practice Bulletin on Pelvic Organ Prolapse

In February 2007, the American College of Obstetricians and Gynecologists (ACOG) published a practice bulletin on pelvic organ prolapse.[373] In the section discussing vaginal mesh kits, it was stated that "Given the limited data and frequent changes in marketed products (particularly with regard to type of mesh material itself, which is most closely associated with several of the postoperative risks, especially mesh erosion), the procedures should be considered experimental and patients should consent to surgery with that understanding." Seven months later, in September 2007, ACOG issued a revision of the practice bulletin on prolapse, in which only one sentence was changed, the sentence quoted above.[374] The new sentence read "Given the limited data and frequent changes in marketed products (particularly with regard to type of mesh material itself, which is most closely associated with several of the postoperative risks, especially mesh erosion), patients should consent to surgery with an understanding of the post-operative risks and lack of long-term outcomes data."

In an interview, the lead author of the practice bulletin, Dr. Weber said she vehemently opposed the change in wording, stating that "I think ACOG was choosing to protect its clinicians' insurance incomes over patients' well being."[375] In a separate article on commercial pressures versus ethics of clinical practice, the authors discussed the change in the ACOG practice bulletin in the context of the proliferation of untested mesh kits for vaginal prolapse surgery, stating that "… powerful commercial interests are attempting to reshape the field of pelvic surgery for their

[372] Jones dep., 727:19-728:4; 728:25-729:10
[373] Weber AM, Smilen SW. ACOG Practice Bulletin on Pelvic Organ Prolapse. *Obstet Gynecol* 2007; 109: 461-473.
[374] Weber AM, Smilen SW. ACOG Practice Bulletin on Pelvic Organ Prolapse [revised]. *Obstet Gynecol* 2007; 110: 717-730.
[375] http://commonhealth.wbur.org/2011/11/surgery-under-scrutiny-what-went-wrong-with-vaginal-mesh, November 4, 2011

financial benefit."[376] In responding to that article, ACOG attempted to explain clinicians' concerns about the "experimental" term by stating that "Their [ACOG Fellows] concerns centered on the ambiguity of the word 'experimental' and their perception that 'experimental' did not accurately reflect the wide acceptance of these surgeries."[377] However, Dr. Weber responded that "Most of the clinicians who objected to the use of the word 'experimental' understood only too well exactly what meaning was intended – that the use of mesh kits as procedures for prolapse lacked sufficient evidence of risk versus benefit to adequately counsel patients as to expected outcomes. Such clinicians were concerned that insurance companies would not cover procedures labeled experimental, and they were concerned about their medicolegal risk should a complication arise in the course of procedures labeled experimental."[378] The fact remains that the original ACOG practice bulletin was correct, and Ethicon had an obligation to explicitly recognize and disclose the experimental nature of the Prolift, which did not occur. Instead, documents and deposition testimony show that Ethicon, including Price St. Hilaire and David Robinson, worked behind the scenes through paid consultants such as Vincent Lucente to get the reference to "experimental" removed.

Of interest, Ethicon informed their Prolift sales representatives to "revisit" this issue with their physicians in case they were avoiding the use of mesh because of the "experimental" nature of the Prolift kit.[379]

The French And U.S. TVM Studies

The clinical studies Ethicon used to support the sale of the Prolift Systems are the so-called French and US TVM studies, which were not performed with the same mesh shapes, instruments, or exact surgical procedure. The TVM studies did not establish the safety and effectiveness of the Prolift Systems. In fact, the French TVM study failed its primary endpoint of 20% or less recurrence rate with only 1 year of follow-up, and the US TVM study met the endpoint by four-tenths of a percentage point only after Ethicon violated the original study protocol and changed the statistical parameters that defined failure versus success, in order to be able to falsely claim that at least one of the TVM studies was a success, and miscounted the recurrences – when correctly counted the US study failed the primary endpoint as well.. (See Medical Literature Review, for detailed discussion of the substantial limitations and shortcomings of the TVM studies.)

[376] Wall LL, Brown D. Commercial pressures and professional ethics: Troubling revisions to the recent ACOG Practices Bulletins on surgery for pelvic organ prolapse. Int Urogynecol J 2009; 20: 765-767.
[377] Lawrence HC. Comments on Wall and Brown: "Commercial pressures and professional ethics: Troubling revisions to the recent ACOG Practices Bulletins on surgery for pelvic organ prolapse." Int Urogynecol J 2009; 20: 1519-1520.
[378] Weber AM. Response to Wall and Brown: "Commercial pressures and professional ethics: Troubling revisions to the recent ACOG Practices Bulletins on surgery for pelvic organ prolapse." Int Urogynecol J 2009; 20: 1523.
[379] ETH-62200, 9-26-2007, email from David Stenftenagel, sales representative: "… Please review the following revised ACOG Technical Bulletin. As you will notice on page 724 the word "experimental" is no longer used. … Please revisit this technical bulletin with your physicians that may have used it as a reason for avoiding the use of mesh for POP due to the "experimental" reference. …"

Overlaying these inadequacies was the complete lack of any long-term studies establishing the safety and effectiveness of the Prolift Systems. In fact, in an article accepted for publication on September 14, 2006, and published thereafter in the International Urogynecology Journal, the French TVM Group recounted numerous complications, and concluded that long-term data were needed to establish the safety and effectiveness of the Prolift Systems – this 1-½ years after the Prolift Systems were first marketed:

> **Anatomical and functional results must be assessed with a long-term follow-up to confirm the effectiveness and safety of the procedure.**[380]

Even to the present day, there are no long-term studies establishing the long-term safety and effectiveness of the Prolift Systems, not to mention the complete lack of long-term studies that describe the safety and effectiveness of the Prolift Systems compared with traditional vaginal prolapse surgery.

If this poorly conceived system comprising the Prolift product and procedure was to be used at all, it should only have been used in the context of a rigorous experimental clinical trial, under strict guidelines, with a limited and carefully circumscribed patient population, and only with an extensive informed consent process designed to clearly notify participants that the use of the Prolift Systems was purely experimental, that the safety and effectiveness could not be reliably stated (hence, the need for clinical study), and that significant, life-altering complications could result, which could be untreatable.

Ethicon's failure to conduct rigorous, long-term clinical study of the Prolift Systems before marketing the product was demonstrates a complete disregard for the health of the women who unknowingly acted as experimental guinea pigs. The result is that women have suffered catastrophic pelvic and vaginal damage, and suffer with permanent, life-altering complications.

Several Ethicon employees, including David Robinson (August 25, 2012), Charlotte Owens (September 12-13, 2012), and Piet Hinoul (September 18-19, 2012), testified that data available at Prolift launch enabled them to conclude that Prolift was safe and effective and therefore warranted marketing of the Prolift Systems. However, on my review of the relevant materials and deposition testimony, it is my opinion that the available data did NOT confirm the safety and effectiveness of Prolift and, in fact, these materials further support my opinion that Prolift was launched before it had been adequately studied, in the face of the existing evidence that the risk benefit profile was unacceptable..

[380] ETH-02358-02367, Fatton BF, Amblard JA, Dabadie CD, Debodinance PD, Cosson MC, Jacquetin BJ. Preliminary results of the Prolift technique in the treatment of pelvic organ prolapse by vaginal approach: a multicentric retrospective series of 110 patients. Int Urogynecol J 2006; 17: s357-360.

For the US TVM study, Ethicon claimed that 12.0% of patients met the study definition of ICS Stage II prolapse or greater by 12 months of follow-up. However, Ethicon failed to include 2 patients[381] with Stage II prolapse at 6 months, patients who met the study's definition of failure by having recurrent prolapse within 1 year of the index TVM procedure. Therefore, the correct frequency of recurrent prolapse by 1 year of follow-up was 12 of 83 patients (14.5%), not 10 of 83 patients (12.0%) as Ethicon falsely claimed. Failure of 14.5%, even with the scientifically inappropriate 90% confidence interval, produced a confidence interval whose upper bound exceeded 20%. Therefore, Ethicon incorrectly claimed that the results of the US TVM study met the pre-defined study criteria, when in fact they did not.

For the French TVM study, Ethicon claimed that 18.4% of patients met the study definition of failure. However, Ethicon failed to include 1 patient[382] with Stage II prolapse at 6 months, who met the study's definition of failure by having recurrent prolapse within 1 year of the index TVM procedure. Therefore, the correct frequency of recurrent prolapse by 1 year of follow-up was 17 of 87 patients (19.5%), not 16 of 87 patients (18.4%) as Ethicon falsely claimed. Even without including this patient, the recurrence rate was so high that the results of the French TVM study failed to meet the pre-defined study criteria of success.

Underestimation of Adverse Events of the TVM Procedure Reported in the Revised Prolift IFU

By reporting the individual frequency of only selected adverse events, Ethicon failed to provide the true extent of complications incurred by women during and after the TVM procedure.

Mesh erosion

Ethicon failed to report the correct number of women with mesh erosion by failing to count mesh erosion that occurred and resolved before the follow-up points of approximately 6 months and 12 months after the TVM procedure. In addition, with regard to the French TVM study data, in a blatant attempt to underestimate the true occurrence of vaginal mesh erosion, Ethicon defined erosions as only those that were visible or visible and palpable, not palpable alone, despite the fact that many patients with palpable mesh erosion required treatment, including surgical treatment..

Moreover, Ethicon failed to define mesh erosion itself in the study protocol, apparently made no attempt to assess or record symptoms caused by mesh erosion, and failed to provide a standardized treatment regimen for mesh erosion in the study protocol.

For the US TVM study, Ethicon inaccurately claimed that mesh erosion occurred in 14.1% (apparently representing 12 of 85 patients), rather than reporting the true frequency of vaginal mesh erosion by 1 year of follow-up in 17% (14 of 83 patients).

[381] Patient numbers 30012, 20027

[382] Patient number 4007

Patients with mesh erosion in the US TVM study included the following:

1. Patient 30001: Surgical (office) treatment of 1×3-mm mesh erosion was performed on 9-17-2004, approximately 2.5 months after the index TVM procedure on 6-30-2004. Surgical treatment of 3×5-mm mesh erosion was performed on 7-27-2005, approximately 13 months after the index TVM procedure. However, no mesh erosion was recorded in Listing 16.2.6.4, Genital prolapse (mesh erosion, operation).
2. Patient 30014: at 1-year follow-up, 1-cm visible mesh erosion at the posterior apex, causing vaginal odor and drainage, treated surgically.
3. Patient 30021: Surgical treatment of 3×2-mm mesh erosion was performed at approximately 6 weeks after the index TVM procedure. However, no mesh erosion is recorded in Listing 16.2.6.4, Genital prolapse (mesh erosion, operation).
4. Patient 10010: at 6-month follow-up, 1-cm visible mesh erosion in the anterior vagina, treated surgically; at 1-year follow-up, 3-cm visible mesh erosion in anterior vagina, treated surgically.
5. Patient 10021: at 1-year follow-up, 2-cm visible mesh erosion in the anterior vagina, treated with surgical resection in the office.
6. Patient 10026: Surgical treatment of 0.5-cm mesh erosion, at site of previous fistula repair, was performed at the time of planned TVT at approximately 6 months after index TVM procedure. However, no mesh erosion is recorded in Listing 16.2.6.4, Genital prolapse (mesh erosion, operation).
7. Patient 20009: at 6-month follow-up, 0.2-cm visible mesh erosion in anterior vagina, no treatment (with regard to the patient's sexual activity, dyspareunia is recorded as

present,[383] yet the record claims that her sexual activity has "no limitation").[384] At 1- year follow-up, "previously visible mesh is now covered with granulation tissue" in anterior vagina, treated with vaginal estrogen.

8. Patient 20010: at 6-month follow-up, 0.2-cm palpable mesh erosion in anterior vagina, no treatment; resolved by 1-year follow-up.
9. Patient 20012: at 6-month follow-up, palpable mesh erosion, no treatment; resolved by 1-year follow-up.
10. Patient 20013: at 6-month follow-up, 1-cm visible mesh erosion in the anterior vagina, "asymptomatic," medical treatment (not otherwise specified); at 1-year follow-up, 1-cm visible mesh erosion in the anterior vagina, medical treatment (not otherwise specified).
11. Patient 20014: The index TVM procedure of anterior and posterior repair with transgluteal sacrospinous fixation was performed on 8-3-2004. Form F41 (convalescence) dated 8-26-2004 at approximately 3 weeks postoperatively indicated a possible rectovaginal fistula; and Form F71 (adverse event) dated 8-26- 2004 indicated mesh erosion. Form F61 (additional gynecologic procedures) dated 9- 14-2004 indicated that the patient underwent posterior mesh removal "to more easily perform rectovaginal fistula repair at a later date." Another Form F61 dated 12-15-2004 indicated that the patient underwent anoscopically directed mucosal flap advancement for the treatment of rectovaginal fistula. At 6-month follow-up, 1- cm visible mesh erosion in the anterior vagina, "asymptomatic," medical treatment (not otherwise specified). However, in Listing 16.2.7.3, Adverse events, the record states that the patient underwent surgical treatment of mesh erosion at approximately 11 months after the index TVM procedure. Mesh erosion was recorded as absent at the 1-year follow-up. New palpable 0.5-cm mesh erosion in the anterior vagina was recorded at 5-year follow-up on 8-11-2009; no treatment was provided.
12. Patient 20019: at 6-week follow-up, "minimal granulation & strands of mesh visible 9/30/04. By 12/9/04 pt [patient] contemplating excision. No treatment initiated."[385] On Form F61 dated 1-10-2005, mesh erosion was treated surgically at approximately 5 months after the index TVM procedure on 8-17-2004. Mesh erosion was recorded as an adverse event in Listing 16.2.7.3.[386] However, no mesh erosion is recorded in Listing 16.2.6.4, Genital prolapse (mesh erosion, operation).
13. Patient 20023: at 6-month follow-up, 1-cm palpable mesh erosion in the anterior vagina, record stated that the patient "declines any treatment"; resolved by 1-year follow-up.
14. Patient 20025: at 6-month follow-up, 1-cm visible mesh erosion at posterior apex, record states that the patient is "without symptoms" yet "some spotting after intercourse and pain with deep penetration only" (dyspareunia was recorded as

[383] ETH-75571
[384] ETH-75564
[385] ETH-75558
[386] ETH-75624

present,[387] yet the patient's sexual activity was recorded as "no limitation"[388]), no treatment; at 1-year follow-up, 1-cm palpable mesh erosion at posterior apex, record states that the patient is "without symptoms" yet "not bothersome" (implying symptoms are present), no treatment.

In addition, 4 patients developed granulation tissue that required medical treatment in all cases, yet these patients were not identified as having an adverse event.[389]

For the French TVM study, Ethicon inaccurately claimed that mesh erosion occurred in 10.0% of patients, in contrast to the true frequency of vaginal mesh erosion by 1 year of follow-up in 22% (19 of 87 patients). The 10.0% figure was based on mesh erosion in 9 patients, using Ethicon's restricted definition of visible mesh erosion and using an inaccurate denominator of 90 patients, rather than the 87 patients who reached 1-year follow-up.

Patients with mesh erosion in the French TVM study included the following:

1. Patient 3004: in Listing 16.2.7.1, Additional operation, the record stated the reason for the procedure was "persistant [sic] exposure of the prosthesis".[390] However, this mesh erosion was not reported in Listing 16.2.6.4, Genital prolapse (mesh erosion, operation).
2. Patient 3006: in Listing 16.2.7.1, Additional operation, the record stated the reason for the procedure was "prosthetic exposure."[391] However, this mesh erosion was not reported in Listing 16.2.6.4, Genital prolapse (mesh erosion, operation).
3. Patient 4002: at 1-year follow-up, 0.5-cm palpable mesh erosion at the vaginal fundus, conservative treatment not otherwise specified.
4. Patient 2002: at 6-month follow-up, "inflammatory tissue without exposure," described as "the little pastille exposed was cut at 6 weeks practically scared [sic] this day." In Listing 16.2.7.3, Adverse events, the record described "exposure of the mesh at the fundus of the vagina" although treatment was not stated.[392] At 1-year follow-up, palpable mesh erosion, no treatment.
5. Patient 5001: at 6-month follow-up, palpable mesh erosion, no treatment; resolved at 1-year follow-up.
6. Patient 5003: at 6-month follow-up, palpable mesh erosion, no treatment; description stated "severe prosthesis retraction"; at 1-year follow-up, palpable mesh erosion, surgical treatment not otherwise specified, description stated "unusual complication with pseudo-tumoral inflammatory reaction on the trigona [trigone]."
7. Patient 5004: at 6-month follow-up, palpable and visible 2-3mm mesh erosion of the posterior vagina, conservative treatment not otherwise specified; at 1-year follow-

[387] ETH-75572
[388] ETH-75565
[389] Patient numbers 20001, 20004, 20022, 20031
[390] ETH-75939
[391] ETH-75939
[392] ETH-75946

up, inflammatory tissue without erosion, conservative treatment not otherwise specified.

8. Patient 5005: at 6-month follow-up, 1-mm visible mesh erosion in the posterior vagina, surgically treated; at 1-year follow-up, no mesh erosion.
9. Patient 5007: at 6-month follow-up, palpable mesh erosion at the vaginal apex, conservative treatment not otherwise specified; at 1-year follow-up, palpable mesh erosion at the vaginal fundus, conservative treatment not otherwise specified.
10. Patient 7002: at 6-month follow-up, palpable mesh erosion with no treatment; resolved at 1-year follow-up.
11. Patient 7003: at 6-month follow-up, palpable mesh erosion with surgical treatment not otherwise specified; at 1-year follow-up, palpable mesh erosion at the "inferior point of the anterior TVM," no treatment.
12. Patient 7005: at 6-month follow-up, note made of "little exposure see [sic] at 6 weeks disappeared." No mesh erosion at 1-year follow-up.
13. Patient 7006: at 6-month follow-up, palpable mesh erosion, no treatment; at 1-year follow-up, palpable mesh erosion described at the anterior portion of the posterior mesh, no treatment.
14. Patient 7010: at 6-month follow-up, palpable mesh erosion, no treatment; at 1-year follow-up, palpable mesh erosion in the inferior part of the anterior mesh, no treatment.
15. Patient 7013: at 6-month follow-up, no mesh erosion; at 1-year follow-up, 1-cm palpable mesh erosion, no treatment.
16. Patient 7014: at 6-month follow-up, palpable mesh erosion, no treatment; resolved at 1-year follow-up.
17. Patient 7019: at 6-month follow-up, palpable mesh erosion in the "interior part of the anterior prothese [prosthesis]" with no treatment; resolved at 1-year follow-up.
18. Patient 8002: at 6-month follow-up, 1-mm visible mesh erosion in the lateral vaginal fundus, conservative treatment not otherwise specified; resolved at 1-year follow- up.
19. Patient 8003: at 6-month follow-up, palpable and visible mesh erosion treated surgically; at 1-year follow-up, no mesh erosion. However, Listing 16.2.7.1, Additional operation, indicated that the patient underwent 2 operations for mesh erosion, the first 119 days and the second 307 days after the index TVM procedure.[393]

Surgical intervention for mesh erosion

Ethicon misrepresented the number of patients requiring surgery for mesh erosion, and nowhere did Ethicon report the number of patients who required more than 1 surgery for mesh erosion.

[393] ETH-75940

For the US TVM study, Ethicon claimed that 7.1% of patients required surgical intervention for mesh erosion. Based on the inappropriate denominator of 85 patients, 7.1% evidently represented 6 patients. First, the correct number of patients requiring surgery for mesh erosion was 8 patients, not 6 patients; and the correct proportion was 8 of 14 patients (57%).[394] Moreover, 3 patients required 2 surgeries for mesh erosion,[395] such that 8 patients underwent 11 operations for mesh erosion within the short-term follow-up of 1 year.

For the French TVM study, Ethicon claimed that 5.6% of patients required surgical intervention for mesh erosion. Based on the inappropriate denominator of 90 patients, 5.6% evidently represented 5 patients. First, the correct number of patients requiring surgery for mesh erosion was 7 patients, not 5 patients; and the correct proportion was 7 of 19 patients (37%).[396] Moreover, 1 patient required 2 operations for mesh erosion,[397] such that 7 patients underwent 8 operations within the short-term follow-up of 1 year.

I. Inconsistent Handling of Prolift Issue Reports

Daniel Lamont, Ethicon director of postmarket surveillance, provided deposition testimony on April 4 and May 24, 2012 as to his responsibility for monitoring the performance of Ethicon's devices in the field. Based on his deposition testimony and documents referenced in this section, I am providing additional analysis of Prolift Issue Reports.

Ethicon received reports of Prolift complaints and complications from sales representatives, physicians, and occasionally patients and recorded these reports as Issue Reports. Some complications were reported; however, the inconsistency in this process resulted in a significant underreporting of Prolift complications.

It must be emphasized that the Prolift Systems represent both a product and a procedure, as clearly described in Ethicon's internal documents and in spite of Ethicon's claims to the contrary in its communications with the FDA. The Prolift product includes the Prolift mesh implant and the single-use inserter tools (cannulas, guides, and retrieval devices) that were designed to perform the Prolift procedure (and only the Prolift procedure). The Prolift procedure, as set out in the Prolift surgical technique document, describes the surgical techniques of Prolift mesh implantation. Therefore, complications that occur during the Prolift procedure ARE device- related, despite Ethicon's claims otherwise. This accounts for some, but not all, of the underreporting of bladder injuries due to the Prolift procedure.

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[394] Patient numbers 30001, 30014, 30021, 10010, 10021, 10026, 20014, 20019
[395] Patient numbers 30001, 10010, 20014
[396] Patient numbers 3004, 3006, 2002, 5003, 5005, 7003, 8003
[397] Patient number 8003

Issue Report	Injury	Reported to FDA
ETH-00490	Bladder injury during dissection, detected after Prolift mesh placement; requiring Prolift mesh removal, bladder repair, and replacement of Prolift mesh	No
ETH-08374	Bladder injury during dissection, requiring repair; native tissue repair performed instead of Prolift mesh placement	No
ETH-08206	Bladder injury during dissection, requiring repair; surgeon changed planned procedure and did not repair anterior vaginal prolapse	Yes
ETH-08108	Bladder injury caused by Prolift cannula placement, requiring repair and extending surgery time	No
ETH-08794	Bladder injury caused by Prolift cannula and mesh placement, requiring repair and extending surgery time	Yes

II. Analysis of Protocol Number 2002-001: Clinical Evaluation of GYNECARE GyneMesh PS Mesh for Pelvic Floor Repair[398]12 (referred to here as the Gynemesh PS mesh study)

In reviewing summaries (white paper, abstracts, posters, and other presentations) and primary data regarding the Gynemesh PS mesh study, it became clear that there were significant discrepancies in, for example, the number of patients at entry and follow-up, the number of patients with mesh erosion, and the number of patients with recurrent prolapse. Therefore, it was necessary to be able to review the September testimony of Piet Hinoul, who was designated as Ethicon's spokesperson as to clinical studies.

When presented with the various summaries of data from the Gynemesh PS mesh study, Dr. Hinoul was unable to reconcile the discrepancies. He testified that he would rely on the peer- reviewed abstract as an accurate representation of the data.[399]

In my opinion, Ethicon designed and performed a scientifically invalid study with pervasive bias, unethical study participant informed consent documents, incomplete and inaccurate data collection, and primary endpoint parameters that endangered patient safety. Ethicon then misrepresented the study's results. This information misled physicians and, thus, patients into unreasonable and inaccurate expectations of the safety and effectiveness of transvaginal Gynemesh PS mesh implantation for prolapse treatment.

[398] ETH.MESH.03736007, protocol approval 2-20-2002

[399] 13 Lucente V et al. A clinical assessment of GYNEMESH PS for the repair of pelvic organ prolapse. J Pelvic Med Surg 2004; 10 (Suppl 1): S35.

This analysis focuses on 78 study participants who underwent prolapse treatment with transvaginal Gynemesh PS mesh implantation.

Overall, the study protocol describing the Clinical Evaluation of GYNECARE GyneMesh PS Mesh for Pelvic Floor Repair is grossly unscientific. The study design is so flawed as to make any of the study's findings scientifically invalid. Strong bias favoring a positive outcome for the product is revealed throughout the study design, from the statement of the study's objective to the lack of independent evaluators of the study's outcomes. The protocol lacks detail and definitions of critical study features. The case report forms are so inadequate that even data on the primary endpoints were not collected accurately or consistently. Mesh erosion was the only adverse event specifically queried on the case report forms; no other mesh-related complications were recorded, in particular, mesh contraction and its clinical consequences. In fact, data were not collected on any other adverse events. Data collection on sexual activity was grossly inadequate and effectively prevented any meaningful analysis with regard to the impact of transvaginal mesh implantation on sexual function.

The following briefly describes the study's shortcomings and deficiencies.

The study's objective is grossly unscientific, as confirmed by Dr. Shott in her evaluation of Ethicon's TVM studies, by stating that the study will "demonstrate" rather than evaluate the use of Gynemesh PS mesh for pelvic floor repair.

The study defined significant mesh erosion, the first of two primary study endpoints, as an erosion that required an operative intervention under anesthesia to address. Erosions that required management with an office procedure without anesthesia were recorded but not included in the primary endpoint. Medical treatment of mesh erosion was not captured at all.

This endpoint of "significant mesh erosion" was defined to minimize the frequency of mesh erosion by only counting erosions that required operative management under anesthesia as "significant." This definition ignored the personal and clinical consequences of mesh erosion in women who did not require operative management under anesthesia. These women experienced symptoms related to their mesh erosion, and from the standpoint of their physical and emotional comfort, an office procedure without anesthesia to treat mesh erosion was likely even more unpleasant than operative management with anesthesia. In addition, this definition of "significant mesh erosion" ignored the women with mesh erosion requiring medical treatment, who experienced symptoms related to their mesh erosion and had to tolerate the risk and bother of medical treatment. Moreover, since most women were treated medically before surgical management, all women who subsequently required surgical treatment for mesh erosion had already gone through medical treatment.

The study protocol did not define the circumstances under which mesh erosion was treated with operative management under anesthesia; given the substantial bias and financial conflict of interest of the surgeon-investigators, it is plausible that the number of women "requiring" operative management under anesthesia for mesh erosion was kept to an artificial minimum to meet the protocol's threshold of "success."

The study defined prolapse recurrence, the second of two primary study endpoints, as ≥ stage II by the ICS POPQ system. Treatment of recurrent prolapse was not included in the definition, which is an important flaw in the study design. Without this inclusion, patients who were surgically retreated within the first year after the index surgery were incorrectly categorized as "successes" if their POPQ measurements at 1 year met the definition of stage 0 or stage I. This occurred with at least 1 patient. Furthermore, anatomic outcomes are not the endpoints of greatest importance to women and do not correlate well with functional outcomes and patient satisfaction. Given that prolapse is a condition that affects quality of life, primary outcomes of prolapse treatment should rely on the patient's experience and impact of treatment on quality of life, rather than relying on arbitrary anatomic outcomes.

Data Collection

Data collection was planned at 4 points. However, study visits that were performed at other times were artificially "allotted" to the timing of the nearest planned study visit, rather than recording and analyzing the data based on the actual duration of follow-up.

Data collection at study entry included surgical history, although the number of previous prolapse surgeries was not collected. Data collection on sexual activity was grossly inadequate, and postoperative assessments were clearly insufficient to obtain any information on sexual activity limited by mesh implantation, including limitations due to mesh erosion, pain, dyspareunia, etc. The only component of data collection related to sexual activity completed by the patient was one question in the quality-of-life assessment that asked whether the above listed symptoms "interfere with my sexual relationships." Only 2 of the listed symptoms applied to prolapse, and the remainder of the symptoms related to voiding and defecatory function.

Therefore, there was no way to determine which symptoms interfered with the patient's sexual activity. This is another example of a serious flaw in study design that produced study results that could not help physicians and women decide whether mesh implantation would satisfactorily address the primary problem of prolapse, including relief from interference with normal sexual activity.

With regard to POPQ measurements that formed the basis of one of the primary outcomes, analysis of data abstracted from the case report forms revealed a disturbingly high frequency of errors in POPQ measurements. One or more errors were seen in 40 of 88 records (45%) at the preoperative assessment; 22 of 85 records (26%) at 3 months; and 17 of 71 records (24%) at 1 year. Clearly, this degree of error would be intolerable in a high-quality study. This high rate of

errors calls into question the validity of results relying on POPQ measurements, including the primary outcome of recurrent prolapse.

Data collection on adverse events was grossly inadequate. Ethicon failed to capture medical treatment as an intervention for mesh erosion. Surgical treatment of mesh erosion was collected haphazardly, if at all. Ethicon failed to collect sufficient information even to allow the categorization of mesh erosion as "significant," one of the two primary study endpoints.
Ethicon utterly failed to collect adverse events following Gynemesh PS mesh implantation in a scientific, unbiased, consistent, and comprehensive way, thereby failing to produce study data that would inform physicians and patients in a fair and balanced way as to what to expect during and after transvaginal mesh implantation as treatment for prolapse.

Subject Informed Consent Forms at the Nine Investigational Sites

The content of the study subject informed consent forms markedly differed across the investigational sites, another indication of Ethicon's poor study design and inadequate standards of study implementation.

With regard to the Gynemesh PS mesh implant, only 3 of the 9 consent forms adequately identified that the mesh implant was permanent, and even in those 3 consent forms, the fact that the mesh implant was permanent was by no means emphasized. In addition, the Gynemesh PS mesh implant was inaccurately described in terms of its development and use in prolapse surgery. The mesh was described as "recently developed" and "recently changed," with no indication that the exact same mesh, Prolene Soft mesh, had been cleared by the FDA in 2000 for use in hernia repair. All but 2 of the consent forms stated that the FDA had evaluated the mesh and used terms including "market release," approval ("approved"), and "clearance" to describe the results of the FDA evaluation. Indeed, one consent form claimed that because the mesh had received FDA clearance, use of the mesh in prolapse surgery "**therefore is not considered experimental**" (bolding in original). By implication or direct statement, almost all of the consent forms described the mesh implantation procedure as standard clinical care, rather than as an experimental procedure. The surgical technique of transvaginal mesh implantation was not standardized. This flawed aspect of study design could only produce a study population from which any results would be difficult to interpret and impossible to replicate.

Even more markedly dissimilar were the descriptions of risks in the subject informed consent forms. Some consent documents claimed that the subjects incurred NO risks by participating in the study, and one consent form listed no risks of research participation at all. The other consent forms identified some risks of transvaginal mesh implantation, although these risks were not consistent across the various investigative sites, and none of the consent forms provided a comprehensive list of risks due to the procedure and permanent transvaginal mesh implantation.

In summary, the content of the study informed consent documents varied markedly at the different investigative sites such that study participants were not provided with consistent and comprehensive information regarding the purpose of the study and the risks of participation.

Women participated in the study voluntarily, based on the assumption that the information that they received under the label of informed consent was complete and accurate. To the marked extent that this was not the case, these women entered the study under false pretenses, with a gross underappreciation of the nature and extent of the risks involved.

Ethicon betrayed the trust these women exhibited as volunteer clinical research participants, in order to obtain sufficient study enrollment to "demonstrate the usability of Gynecare Gynemesh Prolene Soft (polypropylene) mesh for pelvic floor repair." Ethicon acted with unethical and immoral disregard for the health and well-being of these women.

Study Results[400]

In contrast to Ethicon's claims, review of the case report forms revealed that at 3 months, 14% of patients had recurrent prolapse, and 7.2% had mesh erosion. In 1 patient, mesh erosion was treated with 2 outpatient operations under anesthesia; in 1 patient, mesh erosion was treated with office excision; and in the remaining 4 patients, treatment of mesh erosion was not stated.

At 1 year, 26% of patients had recurrent prolapse, including 1 patient who was treated with anterior colporrhaphy 9 months after the index Gynemesh PS mesh implantation procedure.[401] By 1 year of follow-up, a total of 9 of 68 patients (13.2%) experienced mesh erosion. Regarding treatment of mesh erosion, 1 patient had 2 operations; treatment in 5 patients was not stated at all; 1 patient required office mesh excision at both 3-month and 1-year follow-up visits; 1 patient had mesh excision surgery for which no details were provided; and the remaining patient had planned mesh excision surgery for which no details were provided. Therefore, it is impossible to come to any conclusion regarding one of the two primary endpoints of the study, that of "significant mesh erosion," as to its true prevalence and whether this would have resulted in "success" or "failure" of this endpoint as defined in the study protocol. Again, this fact emphasizes the glaring deficiencies in data collection, that any conclusion regarding such an important study endpoint was impossible to draw.

Ethicon's Use of Study Data

Ethicon incorrectly cited these study data in the 2005 Prolift Clinical Expert Report,[402] in which it was claimed that no infections, fistulas, and mesh contraction occurred in this study. In addition, it was claimed that 8 subjects (9.1%) experienced mesh erosion, treated by office intervention with 1 exception, when the true frequency was 13.2%. Moreover, Ethicon misreported the required treatments for the mesh erosions. Ethicon also used these data in an attempt to demonstrate the effectiveness of transvaginal Gynemesh PS mesh implantation in its 2005 professional educational material on the Prolift Systems. Ethicon claimed that after 1 year of follow-up, 16% had prolapse ≥ stage II after transvaginal Gynemesh PS mesh implantation. However, the correct percentage of women with prolapse ≥ stage II at 1 year was 26%.

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[400] ETH.MESH.02411325-ETH.MESH.02413328
[401] ETH.MESH.02412282, patient #9017
[402] ETH-07157-07158

Conclusion

Ethicon designed and performed a scientifically invalid study with pervasive bias, unethical study participant informed consent documents, incomplete and inaccurate data collection, and primary endpoint parameters that endangered patient safety. Ethicon then misrepresented the study's results. This information misled physicians and, thus, patients into unreasonable and inaccurate expectations of the safety and effectiveness of transvaginal Gynemesh PS mesh implantation for prolapse treatment.

The Lack of Prolift Registries

Ethicon failed to establish a data registry for the Prolift that would have enabled it to track the results in real practice. Physicians providing feedback confirmed that data registries are more "reflective of real world experience," because:

> "Clinical studies use Tier 1 docs [doctors], real world experience is heavily weighted with the outcomes produced by Tier 2 and 3 doctors. Data registries more reflect the real world in the eye of many of those docs."[403]

David Robinson resisted a proposal to start a Prolift registry in Australia, confirming in a July 13, 2006 email that this was rejected for commercial reasons. "Consequently, if none of our competitors are keeping registries, our complication data may appear increasingly accurate but with decreasing appeal…"[404]

David Robinson also claimed that the data from the TVM clinical studies was "the most accurate reflection of the occurrence of any adverse events" and a "better means of collection," so it was best to rely on that data.[405] Of course, the TVM studies did not serve the same purpose as a Prolift registry would, in part because the Prolift was not used, and also because the surgeons were probably among the most highly trained with the procedure and would be expected to have the lowest adverse event rates. However, at a meeting in June, 2006, it was decided to differentiate the Prolift procedure from the TVM technique because Professor Jacquetin's success rate was about 80% rather than the hoped for 90% success rate.[406] Finally, in communication with the FDA, Ethicon clearly admitted that the TVM studies did not study the Prolift: "Therefore, no clinical investigations were conducted on the use of Gynecare Prolift Pelvic Floor Repair System."[407]

IX. The Medical Literature

[403] ETH-49659
[404] ETH.MESH.00832920
[405] David Robinson dep., 221:18-222:3; 339:22-340:24.
[406] ETH-82419
[407] ETH.MESH.00372341-00372357

I have reviewed a substantial body of medical literature, which is set forth in the Appendices, as well as referenced in this report. This portion of the report is intended to highlight examples of articles demonstrating the available information regarding the risks and benefits of the use of mesh to repair or augment the repair of hernias and POP (pelvic organ prolapse). As can be seen, the literature in existence before launch of the Prolift product and procedure contained substantial information to alert Ethicon to the risks, complications, and adverse events that would likely be encountered with the Prolift. The literature published since the launch of Prolift further confirms the severe risks, complications, and adverse events caused by the Prolift product and procedure.

In my opinion, Ethicon failed to properly take into account the literature, ignoring negative literature and relying instead on the few "favorable" articles, as well as references that were taken out of context. The result was the marketing of the Prolift without a reasonable basis to support its safety and effectiveness, and with inadequate medical information to physicians and patients.

A. The Hernia Literature

A hernia develops when organs protrude or are at risk of protruding through a weakness or defect of parietal fascia. Parietal fascia is normally a strong layer of tissue, consisting of well-organized and densely packed collagen fibers, that envelops and connects muscles to each other. A weakness or defect in the parietal fascia may be congenital (such as inguinal and umbilical hernias) or acquired (such as incisional hernias).

Ethicon relied to a great extent on the body of literature addressing the use of synthetic mesh, including polypropylene, to repair hernias. Ethicon took the position that this literature supported the safety and effectiveness of the use of mesh to treat POP, despite the fact that (1) this body of literature describes numerous significant risks, complications, and drawbacks of the use of synthetic mesh; (2) the abdominal and female pelvis/vagina are markedly different environments in terms of bacteria, tissue, forces, and planes; and (3) the hernia literature acknowledges the existence of numerous important unanswered questions.

The hernia literature discusses the following significant risks:

1. Infection

The literature with regard to the repair of hernias establishes the risk of infection even in a sterile surgical environment, as bacteria adhere to synthetic materials. There is a risk of infection with permanent mesh implantation even with a low bacterial load. For example,

infection occurred in 7.5% of cases with monofilament mesh and in 30% of cases at a low bacterial load with permanent mesh.[408]

This should have been of tremendous concern to Ethicon since the introduction of a large synthetic mesh through the contaminated field of the vagina was certain to introduce bacteria on the mesh and into the pelvis.

2. Foreign Body Reaction/Inflammatory Reaction to Mesh

The hernia literature establishes that a foreign body reaction occurs with the implantation of polypropylene mesh and that the severity of the foreign body reaction is directly related to the surface area and pore sizes of the mesh implant.[409,410] Moreover, the foreign body reaction to polypropylene mesh is chronic, not transient, and the mesh is certainly not inert.[411,412,413] The literature demonstrates that polypropylene sutures and mesh are not inert and are subject to degradation over time.[414,415,416,417,418, 419,420,421]

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[408] "Without biomaterial [mesh], 50 million micro-organisms were required to cause an infection, whereas in the presence of biomaterial 5 million were enough to cause a wound infection in about 30% of the rats. In all animals, even after dilution down to 50,000 microbes per ml, some bacteria can be detected." Klinge U, Klosterhalfen B. Chapter 15: Biomaterials - experimental aspects. ETH-77160

[409] "… the inflammatory and fibrotic tissue response to polypropylene … depends largely on the total amount of implanted material." Klinge U et al. Impact of polymer pore size on the interface scar formation in a rat model. J Surg Res 2002; 103: 208-214. Epub March 6, 2002. ETH-60811

[410] "The area of contact between the foreign substance and the exposed tissue is an important determinant of the tissue reaction." Cosson M et al. Mechanical properties of synthetic implants used in the repair of prolapse and urinary incontinence in women: which is the ideal material? Int Urogynecol J 2003; 14: 169-178. Epub 25 July 2003. ETH-60792

[411] Chronic inflammatory foreign body reaction at the mesh interface. Klinge U et al. Impact of polymer pore size on the interface scar formation in a rat model. J Surg Res 2002; 103: 208-214. Epub March 6, 2002. ETH-60811

[412] "… PP [polypropylene] … moderate chronic inflammation of the foreign body type with an intense fibrosis. …" Klosterhalfen B et al. The lightweight and large porous mesh concept for hernia repair. Expert Rev Med Devices 2005 Jan; 2: 103-117. ETH-60818

[413] "… macroscopical appearance of explanted meshes being shrunk, folded and rolled and the histological evidence of persistent inflammation over a period of years. Altogether indicate that meshes are not always inertly incorporated. …" "… [fistulas] may develop after 3 months or 15 years." Klinge U, Klosterhalfen B. Chapter 15: Biomaterials - experimental aspects. ETH-77160

[414] Liebert TC et al. Subcutaneous implants of polypropylene filaments. J Biomed Mater Res 1976 Nov; 10(6): 939-951. Degradation begins to occur after only a few days, possibly by the mechanism of auto-oxidation.

[415] Postlethwait RW. Five year study of tissue reaction to synthetic sutures. Ann Surg 1979; 190: 54-57. Sutures implanted in abdominal walls of rabbits and sampled from 6 months to 5 years. Polypropylene sutures showed fragmentation in 4% and perisutural formation of bone, cartilage, or both in 2.6%.

[416] Tuberbille AW et al. Complement activation by nylon- and polypropylene-looped prosthetic intraocular lenses. Invest Ophthalmol Vis Sci 1982; 22: 727-733. Polypropylene activated complement release that mediates acute inflammatory reactions.

[417] Jongeboed WL, Worst JF. Degradation of polypropylene in the human eye: a SEM study. Doc Ophthalmol 1986; 64: 143-152. Polypropylene suture removed after 6.5 years and compared to unused suture. Findings: cracks perpendicular to the longitudinal axis of the suture, part of the surface layer was nearly detached or completely missing; diameter of suture was decreased toward both ends by over 50%; exposed subsurface area layer showed a fibrillar structure. Degradation considered to be caused by the enzymatic action of tissue fluids.

Despite the overwhelming evidence in the medical literature describing the fate of polypropylene mesh *in vivo*, Ethicon continued to claim in the Prolift IFU that "Gynecare Gynemesh PS mesh elicits a minimum to slight inflammatory reaction, which is transient …" and that the mesh is not "subject to degradation."[422] This is an inaccurate statement.

3. Mesh Contraction/Shrinkage

Another well documented risk with hernia mesh is that the mesh contracts as a result of the development of scar tissue exacerbated by the foreign body reaction. The extent of contraction documented with the use of mesh for hernia repairs ranges from approximately 20% to 50%.[423,424,425,426,427,428] Factors though to be related to the extent of mesh contraction include

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[418] "Oxidation would result in surface cracking, decreased melting temperature, loss of mass, and reduced compliance of the material. … the results supported our hypothesis that oxidation is involved with the degradation of polypropylene hernia mesh materials." Costello CR et al. Materials characterization of explanted polypropylene hernia meshes. J Biomed Mater Res B Appl Biomater 2007; 83 (1): 44-49.

[419] Clave A et al. Polypropylene as a reinforcement in pelvic surgery is not inert: comparative analysis of 100 explants. Int Urogynecol J March 2010; 21:261-270. Epub 2010 Jan 6.PLTMEDLIT01605

[420] "… polypropylene (PP) … chemical signs of surface degradation … [in] 55% of … PP explants. The majority of PP … explants demonstrated oxidation … varied degrees of chemical degradation suggesting that lack of inertness in vivo contributes to hernia mesh failure." Cozad MJ et al. Materials characterization of explanted polypropylene, polyethylene terphthalate, and expanded polytetrafluoroethylene composites: spectral and thermal analysis. J Biomed Mater Res B Appl Biomater 2010; 94 (2): 455-462.

[421] Sternschuss G et al. Post-implantation alterations of polypropylene in the human. J Urol 2012 May 12. Epub ahead of print. Degradation by depolymerization, cross-linking, oxidative degradation by free radicals, additive leaching, hydrolysis, stress cracking, and mesh shrinkage along with infection, chronic inflammation, and stimulation of sclerosis. Added substances during manufacture are released through degradation and behave as toxic substances. The material may also absorb various substances. Visibly demonstrable fiber changes resulting in loss of structural integrity through material embrittlement. Heating in manufacture begins the degradation process, augmented by post-production heat to prevent curling and attach appendages.

[422] ETH.MESH.02341526, original Prolift IFU; ETH.MESH.02341737, Prolift IFU revised after FDA review

[423] "Contraction of the mesh fibers during the scarring process leads to shrinkage of the mesh after implantation in vivo. Radiographic measurements of the distances between the metallic staples used for the pre-peritoneal mesh repair of incisional hernias made 10 months after implantation revealed contraction of approximately 20% when compared to measurements taken shortly after the procedure." Amid PK. Classification of biomaterials and their related complications in abdominal wall hernia surgery. Hernia 1997; 1:15-21. PLTMEDLIT00681

[424] Klinge U et al. Shrinking of polypropylene mesh in vivo: an experimental study in dogs. (46%) Eur J Surg Dec 1998; 164:965-969.

[425] "All available meshes, regardless of their composition, experience a 20% to 50% reduction in their initial size." Cobb WS et al. The argument for lightweight polypropylene mesh in hernia repair. Surg Innov 2005 March; 12: 63-69. ETH-60872 (PLTMEDLIT01600)

[426] Using a pig model of hernia repair, there was no difference in mesh contraction after 5 months, 28% for heavyweight mesh (Marlex), 33% for midweight mesh (Prolene Soft), and 29% for lightweight mesh (Ultrapro). Cobb W et al. Textile analysis of heavy-weight, middle-weight and light-weight polypropylene in porcine ventral hernia repair. J Surg Res Nov 2006; 136: 1-7. Epub 9-22-06. ETH-47802

[427] Vega-Ruiz V et al. Surveillance of shrinkage of polypropylene mesh used in the repair of ventral hernias [Spanish]. (12% at 1 month, 24% at 3 months, 29% at 6 months, 34% at 12 months) Cir Esp 2006; 80: 38-42. Abstract in English.

various mesh characteristics, such as mesh weight and pore size. However, mesh weight is considered less important than pore size or porosity (see further discussion below). In one study, mesh contraction of 28% to 33% did not differ when comparing polypropylene meshes of heavy weight (Marlex), mid-weight (Prolene Soft), and light weight polypropylene-poliglecaprone (Ultrapro).[429]

It is also established that mesh contraction leads to a reduction in pore size *in vivo*. In one study, loss of pore size occurred in proportion to the extent of mesh contraction.[430] To counteract this effect, hernia mesh is commonly placed to overlap the size of the hernia defect by at least 5 cm on each side.[431,432] This was not taken into account during design of the Prolift procedure and indeed is not an option with the Prolift procedure.

In an important study, it was concluded that pore sizes "should exceed a distance of 1000 µm [1 mm] between two polypropylene filaments," to prevent fibrotic bridging while allowing the necessary tissue integration.[433] Utilizing the term "effective porosity," one can establish the portion of the implant that has pore sizes that exceed 1000 µm (1 mm). The authors explained the clinical significance:

Porosity of textile implants seems to be the main determent for tissue reaction. Widely independent of the polymer the construction of pores enhances the inflammatory and fibrotic response, getting more intense with reduction of pore size. … Correspondingly, only pores with a diameter of >1000 µm are regarded as appropriate, resulting in an "effective porosity," which is often considerably less than assumed. With a filter of a minimum pore size of 1000 µm, the effective porosity of some structures sometimes even vanishes completely. …
It has to be considered that any mechanical strain may lead to deformation of the textile and thereby reduces the effective porosity markedly.

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[428] Garcia-Urena MA et al. Differences in polypropylene shrinkage depending on mesh position in an experimental study. (mesh area reduced by 26% on day 30, 29% on day 60, 29% on day 90) Am J Surg 2007; 19: 538-542.
[429] ETH-47802: Cobb W et al. Textile analysis of heavy-weight, middle-weight and light-weight polypropylene in porcine ventral hernia repair. J Surg Res 2006; 136: 1-7. Presented at Association for Academic Surgery, November 2004.
[430] "Furthermore, comparison between mesh removed from patients and processed through an alcohol-methyl salicylate clearing sequence with that of a control demonstrates that the pore sizes of the removed mesh are approximately 20% smaller." Amid PK. Classification of biomaterials and their related complications in abdominal wall hernia surgery. Hernia 1997; 1:15-21. (PLTMEDLIT00681) (reduction proportional to extent of mesh contraction)
[431] "Shrinkage … Sufficient long-term hernia repairs can only be performed with large meshes overlapping the hernia gap by a minimum of 5 cm each side." Klosterhalfen B et al. The lightweight and large porous mesh concept for hernia repair. Expert Rev Med Devices 2005 Jan; 2: 103-117. ETH-60818
[432] "Failure of hernia repairs nearly always occurs laterally at the mesh-tissue interface because of a failure of fixation, incorporation, or lack of overlap." Cobb WS et al. The argument for lightweight polypropylene mesh in hernia repair. Surg Innov 2005 March; 12: 63-69. ETH-60872
[433] Muhl, et al. New Objective Measurement to Characterize the Porosity of Textile Implants. J. Biomed Mater Res Part B: Appl Biomater 84B:176-183, 2008 (ETH.MESH.02184131).

In a recent study, Klinge and Klosterhalfen used the 1000-µm threshold to categorize mesh types by porosity, because "for polypropylene meshes this is the least distance that prevents bridging of scar tissue, which then fills out the entire pore."[434] The authors emphasized the difference between textile porosity, a laboratory measurement that describes the area not covered by the mesh fibers (the proportion of empty space between mesh filaments), versus effective porosity, an *in vivo* measurement of the area of "good" pores where bridging of scar tissue is avoided by sufficient interfilamentary distance. In one example, the company-reported textile porosity of 68% dropped to 42% when measured as effective porosity.

Ethicon described Gynemesh PS and the Prolift as "large pore" consistent with Amid Type I mesh.[435] It is important to recognize that the knitting process results in irregular pore geometries and sizes; as such even though Gynemesh PS has some large pores, it has a range of pore sizes down to measured sizes as small as 0.29mm and smaller.[436] Nonetheless, Ethicon described an average pore size of Gynemesh PS of 2.5mm,[437] while knowing it was inappropriate to claim a distinct pore size.[438] The key, as set forth herein, is that the polypropylene mesh needs to have a high enough number of/percentage of pores greater than 1 mm in all directions, upon implantation, to prevent fibrotic bridging, and consequential related complications such as erosion and exposure. Some experts believe that, when vaginal mesh exposure occurs, the entire mesh is likely to be affected and that the exposure itself represents only "the tip of the iceberg." In that case, experts consider it "unlikely that simple excision or [vaginal] placement of estrogen will be successful over the long term"[439] in managing vaginal mesh exposure. In fact, this is the likely explanation when women require multiple mesh excision procedures for persistent or recurrent mesh exposure.

These issues were not considered by Ethicon. Ethicon never performed testing to determine what effect implantation of the Prolift polypropylene mesh into a patient during vaginal prolapse surgery would have on pore size. (Clifford Volpe dep., 361:1-8). In addition, despite the different clinical indications (repair of abdominal hernia versus vaginal repair of

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[434] Klinge U, Klosterhalfen B. Modified classification of surgical meshes for hernia repair based on the analyses of 1,000 explanted meshes. Hernia DOI 10.1007/s10029-012-0913-6.

[435] PLTMEDLIT00681: Amid PK. Classification of biomaterials and their related complications in abdominal wall hernia surgery. Hernia 1997; 1:15-21.

[436] ETH-83788, 1-26-2006: "Typical Pore Size: Range of pore sizes (mm2) in Prolene Soft mesh: 0.29, 0.34, 1.08, 1.29, 1.70, 2.38"

[437] ETH-70372 (2.5 mm), ETH-76220 (1750 × 2530 microns), ETH.MESH.00000077 (2.4 mm), ETH.MESH.00018382 (1750 × 2530 microns)

[438] ETH.MESH.01431617, 6-14/15-2006, email chain about Gynemesh PS/Prolene Soft mesh pore size, Robert Rousseau: (Ethicon principal engineer): "Pore size in microns was not measured during the development of the Prolene Soft Mesh. The total percent area that is open was measured and is considered an accurate method. Since the product construction results in irregular pore geometries and size, it is not accurate to report a distinct pore size." Elizabeth Vailhe 6-15-2006: "I agree with Bob's comments below. Our database contains the percent porosity numbers and not the individual pore size. …"

[439] Roundtable: Using mesh to repair prolapse: Averting, managing complications. Karram MM, moderator. OBG Management 2009; 21 (2): 21-28.

prolapse) and markedly different surgical environments, Ethicon never tested how Gynemesh PS mesh would behave after implantation during vaginal prolapse surgery.[440]

4. Mesh-Related Chronic Pain

Chronic pain is a well-known consequence of mesh implantation in hernia repair, with the reported frequency ranging from 0% to 37%. In a meta-analysis of randomized trials of hernia repair, chronic pain was reported in 5% of patients after mesh-based hernia repair, although there was substantial heterogeneity between studies as to the prevalence and definition of pain.[441] The etiology of this chronic pain has been attributed primarily to nerve damage resulting in neuropathic pain, although other mechanisms may play a role as well. Such pain is documented to be long-lasting if not permanent and severe enough in many patients to interfere with daily activities. For example, one series of articles reported pain and functional impairment 1 year and 6 years after inguinal herniorrhaphy. At 1 year, more than one-quarter of patients (28.7%) still experienced pain, and the pain was severe enough to interfere with daily activities (functional impairment) in more than half of those with pain.[442] At 6 years, in patients with no subsequent hernia repair, more than one-third (34.3%) had persistent pain, and the pain interfered with daily activities in almost three-quarters (72.2%) of people with pain.[443] The pain was the same or worse in nearly one-quarter of the patients (24.2%). In patients who had another hernia repair in the intervening 5 years, one-half of the patients experienced chronic pain, and pain limited daily activities in 80% of those.

Treatment options are limited when chronic pain occurs after mesh-based hernia repair. One article described surgery in 20 patients with severe pain; all 20 patients had mesh removal, and 16 of 20 patients also had nerve resection (neurectomy).[444] Only 60% experienced symptom resolution. The authors coined a new term to describe this syndrome, "inguinodynia," and concluded that "Correcting this problem once presented can be a formidable task."

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[440] ETH.MESH.01160159, Gynemesh Prolene Soft mesh, pre-clinical functionality testing strategy, 11-1-2001, Histology: "… This product [polypropylene] is not subject to degradation over time. Based on the results of animal testing performed on Prolene sutures and mesh, it is expected that initially following surgical placement of Gynemesh Prolene Soft mesh there will be a transient slight inflammatory reaction. A thin layer of fibrous connective tissue will then cover the mesh and penetrate the interstices. The clinical tissue compatibility of Gynemesh Prolene Soft mesh is essentially equivalent to Prolene mesh since the Gynemesh Prolene Soft mesh is chemically unchanged from Prolene mesh and sutures." Conclusion: "Based upon the Gynemesh Prolene Soft mesh's product characteristics, intended clinical indications and the use of existing polymer materials, additional pre-clinical functionality testing is not required."

[441] EU Hernia Trialists Collaboration. Repair of groin hernia with synthetic mesh: meta-analysis of randomized controlled trials. Ann Surg 2002; 235: 322-332.

[442] Bay-Nielsen M et al. Pain and functional impairment 1 year after inguinal herniorrhaphy: a nationwide questionnaire study. Danish Hernia Database. Ann Surg 2001; 233: 1-7.

[443] Aasvang EK et al. Pain and functional impairment 6 years after inguinal herniorrhaphy. Hernia 2006; 10: 316-321. Epub May 19 2006.

[444] Heise CP, Starling JR. Mesh inguinodynia: a new clinical syndrome after inguinal herniorrhaphy? J Am Coll Surg 1998; 187: 514-518.

Given this experience with mesh-based hernia repair, Ethicon had to have expected similar, if not worse, outcomes after transvaginal mesh implantation in prolapse surgery (the TVM and Prolift procedures). Indeed, as early as the first TVM study, Ethicon knew that patients were at risk for pain that was severe, long-lasting if not permanent, and refractory to treatment.[445] Nevertheless, the original Prolift IFU did not even contain the word "pain" as one of the possible adverse reactions.[446]

5. Mesh Exposure/Erosion/Sinus Tract Formation

True mesh exposure is uncommon after mesh-based hernia repair, likely due to the thickness of the overlying tissue layers. Mesh erosion into viscera (such as small bowel and large bowel) occurs rarely, although large-pore meshes are more prone to cause this complication.[447] When mesh erosion into bowel occurs, fistula formation is likely, often with drainage of intestinal contents to the skin surface; aggressive surgical management is always required.[448] Sinus tract formation results from chronic infection of the underlying mesh and drainage of purulent material to the skin surface. One series reported sinus tract formation in 5% of patients after mesh-based incisional hernia repair.[449]

Analogous to sinus tract formation after mesh-based hernia repair, vaginal mesh exposure after transvaginal mesh implantation in prolapse surgery may represent chronic mesh infection with the formation of a "sinus tract" to the "skin surface," that is, the vagina itself. This may explain, in part, why some women develop persistent or recurrent mesh exposure after simple excision of the vaginally exposed mesh. Despite its high frequency after the Prolift procedure, Ethicon never studied vaginal mesh exposure to determine its etiology or any effective means of prevention and management.

The abdomen and female pelvis/vagina are markedly different environments in terms of bacteria, tissue, forces, and planes.[450] Relative to permanent synthetic mesh implantation, these differences include the clean versus clean-contaminated surgical conditions; the composition and thickness of layers overlying mesh implants; forces that act upon the mesh after implantation and

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[445] ETH-75940

[446] ETH.MESH.02341522

[447] PLTMEDLIT00681: Amid PK. Classification of biomaterials and their related complications in abdominal wall hernia surgery. Hernia 1997; 1:15-21. "Another undesirable side effect of macroporous materials [defined as pore size > 75 microns] is erosion and migration of the prosthesis into the gastrointestinal tract when they are in direct contact with the intestines. This complication is even more common when the prosthesis is in direct contact with organs without serosal covering: the distal esophagus, rectum, bladder, and denuded intestinal tract."

[448] Miller K, Junger W. Ileocutaneous fistula formation following laparoscopic polypropylene mesh hernia repair. Surg Endosc 1997; 11: 772-773.
Fernandez Lobato R et al. Colocutaneous fistula due to polypropylene mesh. Hernia 2001; 5: 107-109.
Aldridge AJ, Simson JN. Erosion and perforation of colon by synthetic [polypropylene] mesh in a recurrent paracolostomy hernia. Hernia 2001; 5: 110-112.

[449] Basoglu M et al. Late complications of incisional hernias following prosthetic mesh repair. Acta Chir Belg 2004; 104: 425-428.

[450] ETH.MESH.00164607: "The vagina is NOT the abdomen (nor similar to any other surgical environment)"

geometric planes in which the mesh is implanted; and relevant variations in bony and soft tissue anatomy.

When surgery is performed in or through the abdominal wall, the surgical environment is considered clean. Postoperative wound infection is minimized by the use of systemic perioperative antibiotics, preoperative skin cleansing with antibacterial solution, and sterile surgical draping. In contrast, surgery performed in or through the vagina is considered clean-contaminated. Two of the same strategies are used to minimize postoperative infection, including systemic perioperative antibiotics and preoperative vaginal cleansing. Because the vagina is replete with normal bacterial and fungal inhabitants, it is not possible to "sterilize" the vagina in preparation for surgery.[451] In addition, it is not possible to use sterile surgical draping in such a way as to limit microbial contamination of the surgical field. For these reasons, microbial contamination of any permanent synthetic mesh implant is inevitable. Based on this situation alone, Ethicon should have studied the body's reaction to Gynemesh PS mesh when used at vaginal prolapse surgery. Ethicon failed to do any studies of this nature, as noted above, based simply on the assumption that there was no need to perform testing since the chemical composition of Prolene Soft mesh and Gynemesh PS mesh was the same.[452]

Another important difference relative to permanent synthetic mesh implantation in the abdominal wall versus the vagina is the thickness of the overlying tissue layers. The abdominal wall consists of the peritoneum, several muscle groups surrounded by a strong layer or layers of parietal fascia, a variable amount of subcutaneous fat, and skin. During abdominal hernia repair, the mesh can be placed between the peritoneum and fascia (sublay) or above the fascia (onlay). The results of animal studies demonstrate less mesh contraction, less inflammatory response, and better tissue incorporation with mesh implantation in the sublay (deeper) location.[453] Depending on the amount of subcutaneous fat, the tissue covering the mesh implant is at least a few and often several centimeters thick. In contrast, the vagina consists of 2 layers, epithelium and muscularis (smooth muscle), enveloped by visceral ("endopelvic") fascia. The endopelvic fascia is a common layer between the vagina and bladder anteriorly, termed the vesicovaginal space, and between the vagina and rectum posteriorly, termed the rectovaginal space. During traditional vaginal surgery, the appearance of "pubocervical fascia" anteriorly and "rectovaginal fascia" posteriorly occurs due to dissection of the vaginal epithelium from the underlying layers. Unfortunately, this use of the term "fascia" for both parietal and visceral fasciae has caused some confusion in the minds of surgeons as to differing natures of these tissues. Visceral fascia is

[451] PLTMEDLIT01559: Culligan P, Heit M, Blackwell L, Murphy M, Graham CA, Snyder J. Bacterial colony counts during vaginal surgery. Infect Dis Obstet Gynecol 2003; 11: 161-165.

[452] ETH.MESH.01160159, Gynemesh Prolene Soft mesh, pre-clinical functionality testing strategy, 11-1-2001, Histology: "…The clinical tissue compatibility of Gynemesh Prolene Soft mesh is essentially equivalent to Prolene mesh since the Gynemesh Prolene Soft mesh is chemically unchanged from Prolene mesh and sutures." Conclusion: "Based upon the Gynemesh Prolene Soft mesh's product characteristics, intended clinical indications and the use of existing polymer materials, additional pre-clinical functionality testing is not required."

[453] Garcia-Urena MA et al. Differences in polypropylene shrinkage depending on mesh position in an experimental study. Am J Surg 2007; 19: 538-542.
Binnebosel M et al. Impact of mesh positioning on foreign body reaction and collagenous ingrowth in a rabbit model of open incisional hernia repair. Hernia 2010; 14: 71-77. Epub Nov 5 2009.

distinctly different than parietal fascia. In contrast to the strong and well-ordered collagen layers of parietal fascia, visceral fascia consists of loose irregular collagen and small amounts of fatty tissue.[454] The blood vessels and nerves of the pelvic organs travel through the endopelvic fascia to reach their respective organs. Estrogen deficiency from natural or surgical menopause results in vaginal atrophy. With advanced prolapse, the vaginal epithelium can become thickened. During the Prolift procedure, the Gynemesh PS mesh is implanted in the vesicovaginal and rectovaginal spaces, beneath the vaginal epithelial and muscularis layers. The thickness of these layers may vary by a few millimeters but will never be more than a centimeter thick, and most of the time, the thickness will be less than a centimeter. This dramatic difference in the tissue thickness covering the mesh implant in the vagina versus the abdomen probably explains, in part, some of the difference in mesh-related complications, particularly the high frequency of vaginal mesh exposure. Nothing in the design or development of the Prolift procedure accounted for this dramatic difference in tissue thickness over the mesh implant, and Ethicon never studied the effect of overlying tissue thickness and mesh-related complications in a clinical or preclinical setting in any way and certainly not with an adequate proxy for mesh implantation in vaginal prolapse surgery.

Permanent synthetic mesh implants are affected by forces that act upon the mesh after implantation, which depend in part on the geometric planes in which the mesh is implanted. The abdominal wall is a relatively simple structure. For many cases of abdominal hernia repair, the hernia defect is approximately two-dimensional, and the repair can be performed with a flat mesh, usually of rectangular shape. The forces acting on the mesh, primarily intra-abdominal pressure, have been well characterized at rest and during various activities that can affect intra-abdominal pressure. However, forces and geometrical factors in the pelvis are not nearly as well understood or easy to measure, particularly in women with pelvic organ prolapse. Even with normal support, the vagina itself has a complex three-dimensional anatomy, approximately H-shaped in cross-section; added to that are the normally independent three-dimensional shapes of the bladder and rectum, plus close interrelations between the pelvic muscles, connective tissue, and large neurovascular structures traveling to and through the pelvis. These aspects of normal anatomy are vastly altered with prolapse, with displacement of the vagina and adjacent organs, distortion of the size and shape of the vagina, and altered relations between the rest of the pelvic structures. There is no standardized way to assess vaginal pressure; various methods have been attempted, including digital palpation, vaginal cones (small cone-shaped devices of different weights), and vaginal closure pressure.[455] In normal women, the vaginal entrance is kept closed

[454] Weber AM, Walters MD. Anterior vaginal prolapse: review of anatomy and techniques of surgical repair. Obstet Gynecol 1997; 89: 311-318.

[455] Hahn I et al. Comparative assessment of pelvic floor function using vaginal cones, vaginal digital palpation, and vaginal pressure measurements. Gynecol Obstet Invest 1996; 41: 269-274.

PLTMEDLIT01398: Mouritsen et al. Vaginal pressure during daily activities before and after vaginal repair. Int Urogynecol J 2007; 18: 943-948. Epub 2007 Jan 18.

Peng Q et al. Spatial distribution of vaginal closure pressures of continent and stress urinary incontinent women. Physiol Meas 2007; 28: 1429-1450. Epub 2007 Oct 12.

Shishido K et al. Influence of pelvic floor muscle contraction on the profile of vaginal closure pressure in continent and stress urinary incontinent women. J Urol 2008; 179: 1917-1922. Epub 2008 Mar 18.

by inherent tone and voluntary action of the pelvic and perineal muscles. In women with prolapse, the vaginal opening may be gaping due to dysfunction of the muscles and protrusion of the prolapse itself. Forces that act on the pelvis have not been established for women with normal support or for women with prolapse. In addition, as Ethicon has acknowledged, "in vivo forces and exerted strains on pelvic floor repairs during the post operative period are not known."[456] Without understanding forces affecting the pelvis with normal support, with prolapse, or after permanent synthetic mesh implantation, Ethicon had no way of knowing whether Gynemesh PS mesh had the necessary characteristics to safely and effectively restore pelvic support. Despite this, Ethicon made several unsubstantiated claims about the Gynemesh PS mesh implant in the Prolift IFU and sales aids directed to patients.[457] Ethicon never performed any studies to obtain this critically important information regarding the pelvic forces acting on the Prolift mesh implant; as noted above, Ethicon did no studies at all when they took the hernia mesh, Prolene Soft mesh, and applied it to vaginal prolapse surgery, merely renamed it Gynemesh PS mesh. Furthermore, Ethicon performed no studies to obtain this information when another hernia mesh, Ultrapro, was chosen as a substitute for the Prolift mesh and renamed Gynemesh M mesh.

Every individual has a certain level of variation in their anatomy. As discussed above, the abdominal wall is a relatively simple structure, and mesh implantation is performed under direct visualization so the surgeon can see and avoid structures at risk. Again, as previously noted, pelvic anatomy is very complex, and the blind passage of the Prolift's trocars prevents direct visualization and avoidance of key structures, particularly large neurovascular structures traveling to and through the pelvis. Furthermore, individual patient variations in pelvic bony and soft tissue anatomy cannot be visualized by the surgeon. Design and development of the Prolift procedure did not take into account this type of anatomic variation. Studies have identified key variations in bony pelvic anatomy relevant to the Prolift procedure. One study described that the length of the obstetric conjugate was directly related to the distance from the ischial spine to the medial border of the sacrum (consistent with the length of the sacrospinous ligament), thereby influencing the location of safest passage when using the sacrospinous ligament as a fixation point for support of the vaginal apex.[458] Despite this, the Prolift surgical technique document describes passage of the posterior trocar at a fixed distance from the ischial spine, not taking into account the variation between individuals.[459] Another study described considerable variation in bony anatomy of the obturator foramina and pubic bones related to race and height of the

[456] ETH-07156, Prolift Clinical Expert Report, 1-14-2005
[457] ETH.MESH.02341523, Original Prolift IFU: "The bi-directional elastic property allows adaptation to various stresses in the body." After FDA review, Ethicon was forced to delete this statement for lack of evidence.
ETH.MESH.02341523 and ETH.MESH.02341736, Original and revised Prolift IFUs: "The mesh affords excellent strength, durability, and surgical adaptability, with sufficient porosity for necessary tissue ingrowth."
ETH.MESH.00016663, Prolift patient brochure: "The strength of this tissue is greatly enhanced by the presence of the soft mesh."
[458] Verdeja A et al. Transvaginal sacrospinous colpopexy: anatomic landmarks to be aware of to minimize complications. Am J Obstet Gynecol 1995; 173: 1468-1469.
[459] ETH.MESH.00419581

individuals.[460] Nevertheless, the Prolift surgical technique document describes placement of the skin incisions for passage of the superficial and deep anterior trocars based on the level of the urethra;[461] the location of the urethra itself no doubt varies, particularly in relation to the type and degree of prolapse present, but that type of soft tissue variation does not account for variation in bony anatomy.

The hernia literature acknowledges the existence of numerous unanswered questions, most importantly, the type and characteristics of the ideal mesh implant. The approach to hernia repair has evolved over the years, from suture repair that was sometimes not possible in the cases of very large fascial defects, to the use of metallic meshes through the 1950s, and the introduction of synthetic meshes such as polypropylene and polyethylene beginning in the late 1950s. Although hernia recurrence decreased, "heavyweight" synthetic meshes brought their own share of complications, including intense inflammation, mesh shrinkage, and reduced abdominal wall compliance. In the 1990s, general surgeons began to wonder if heavyweight mesh was "over-engineered" and if lighter-weight mesh would meet the needs of hernia repair while decreasing the complication rate. Since that time, the number of materials for use in hernia repair has exploded, with one recent article estimating that 166 different devices are marketed for hernia repair.[462] Such a profusion of devices clearly indicates that the ideal mesh implant for hernia repair has yet to be identified; once the ideal mesh implant was identified, it would supplant all other materials as surgeons (and patients) recognized its superiority.

Similarly, the ideal mesh implant for vaginal prolapse surgery has yet to be identified (if, in fact, one exists at all). In 2002, Dr. Arnaud, Scientific Director of Europe Gynecare, gave a presentation in which he enumerated 5 requirements for mesh used in vaginal prolapse surgery. He stated that the mesh: 1) must resist infection; 2) must incorporate with rather than encapsulate the surrounding tissue; 3) must be histologically well tolerated; 4) must not shrink; and 5) must be soft.[463] Although the presentation was clearly biased and promotional toward Gynemesh PS mesh, abundant evidence argues against the idea that Gynemesh PS mesh is the ideal mesh implant for vaginal prolapse surgery.

1) Gynemesh PS mesh has no specific characteristics that would enable it to resist infection. Indeed, as discussed above, given the inevitable microbial contamination at vaginal surgery and the mesh's irregular pore size and interstices that harbor bacteria while preventing access to immune cells, Gynemesh PS mesh has characteristics that may indeed potentiate infection, despite Ethicon's marketing claims to the contrary. And, in fact, IFUs for Gynemesh PS mesh and Prolift identify infection potentiation as an adverse

[460] Ridgeway BM et al. Variation of the obturator foramen and pubic arch of the female bony pelvis. Am J Obstet Gynecol 2008; 198: 546.e1-4.
[461] ETH.MESH.00419576, ETH.MESH.00419578
[462] Klinge U, Klosterhalfen B. Modified classification of surgical meshes for hernia repair based on the analyses of 1,000 explanted meshes. Hernia 2012; Epub 5-5-2012. DOI 10.1007/s10029-012-0913-6.
[463] ETH.MESH.PM.000011

reaction.[464] (See below for further discussion of Ethicon's claim regarding infection potentiation with Gynemesh PS mesh.)

2) As to the requirement that mesh incorporate into the surrounding tissue instead of be encapsulated by the surrounding tissue, Ethicon has never studied the specific tissue response elicited by Gynemesh PS mesh when implanted during vaginal prolapse surgery. Nevertheless, Ethicon acknowledged the deficiencies of Gynemesh PS mesh in this regard, and others, in documents preparing for the launch of the Prolift + M Systems, in which the hope was expressed that Gynemesh M mesh (Ultrapro) would meet all the needs of vaginal prolapse surgery since it was evident that Gynemesh PS mesh (Prolene Soft) did not.[465]
3) No form of polypropylene mesh, including Gynemesh PS mesh, is histologically well tolerated; as described in detail elsewhere in this report, Gynemesh PS mesh elicits a chronic inflammatory and foreign body reaction, which depends at least in part on the amount of mesh burden that the body is exposed to. A larger surface area of mesh elicits a more severe inflammatory and foreign body reaction.
4) All forms of polypropylene mesh, including Gynemesh PS mesh, shrink (or contract or retract) as part of the natural healing process during which scar tissue shrinks as collagen matures. However, in the presence of Gynemesh PS mesh, healing is not natural, at least in part due to the chronic inflammatory and foreign body reaction. Mesh shrinkage is exaggerated in direct relation to the severity of the inflammatory and foreign body reaction.
5) "Softness" is not a mesh characteristic per se; rather, it is a perception on the part of the surgeon handling the mesh. Describing a permanent synthetic mesh such as polypropylene as "soft" is counterintuitive and misleading, as if this "softness" bears any relation to the characteristics of the normal vaginal tissue and the body's chronic inflammatory reaction to this foreign body. Axel Arnaud testified in his deposition that the idea that mesh will remain soft after implant is an illusion.

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[464] ETH.MESH.02342194, ETH.MESH.02341522

[465] ETH-60667, 10-29-2008, email from Jonathan Meeks to Scott Jones: "Key Point: PP [polypropylene] is the best of a bad lot re integration, retraction and there is a need to develop grafts that mimic the human tissue mechanical properties."

ETH.MESH.00001372, 2009 AUGS briefing deck with a set of 9 slides promoting Prolift + M:

Mesh that behaves "MORE like native tissue"

- MORE flexibility
- Improved tissue integration

The obvious implication being that Prolift (Gynemesh PS mesh) behaves LESS like native tissue, has LESS flexibility, and WORSE tissue integration (not that Ethicon had any evidence for these Prolift + M claims either).

ETH.MESH.00267992, 12-12-2006, Lightning [previous name for Prolift + M] project charter, Unmet need: Minimize shrinkage, vaginal stiffness, dyspareunia and permanent pain; lower the rate of [prolapse] recurrence due to less tissue contraction; minimize [vaginal mesh] exposure.

The obvious implication being that Prolift (Gynemesh PS mesh) was causing too much and/or too frequent episodes of shrinkage, vaginal stiffness, dyspareunia and permanent pain; too frequent prolapse recurrence due to tissue contraction; and too frequent vaginal mesh exposure.

Ethicon ignored the documented problems with the use of permanent synthetic mesh to repair abdominal hernias and relied only on the possibility that the use of such mesh could result in a durable long-lasting repair when used in vaginal prolapse surgery. Ethicon should have done extensive preclinical testing to try to understand how the use of permanent synthetic mesh, particularly the polypropylene mesh intended for use in the Prolift procedure, would perform in the female pelvis. If such testing had supported a valid conclusion that the use of the Prolift would be safe and appreciably more effective than traditional non-mesh repairs of POP, then an experimental clinical study should have been launched, under strict protocols and with extensive informed consent, to study the safety and effectiveness of the Prolift polypropylene mesh in actual use, as suggested by Charlotte Owens, M.D. in her first draft of the Prolift Clinical Expert Report. Such a study would need follow-up for a sufficiently long period to ensure that a decision to market the permanent mesh implant would be based on enough years of study to understand the long-term effects on women. Women as young as in their 30s have had implantation of the permanent Prolift polypropylene mesh, with life expectancy of an additional 50 years or more. With that expectation in mind, results of extremely short-term animal studies, on the order of weeks, cannot possibly provide sufficient evidence of safety; in addition, the results of animal studies mimicking abdominal hernia repair have no relevance in assessing safety with regard to the use of Prolift polypropylene mesh in vaginal prolapse surgery.

There are different requirements for pelvic organ function after a Prolift procedure versus function after abdominal hernia mesh repair, including the need to maintain independent function of the bladder, rectum, and vagina. The bladder and rectum must be able to expand and contract independently of the vagina. Normally, these cycles of filling and emptying are permitted by the expansile layer of adventitia (endopelvic fascia) between the bladder and vagina (vesicovaginal space) and the rectum and vagina (rectovaginal space). However, mesh implantation in the vesicovaginal and rectovaginal spaces in the Prolift procedure can prevent or interfere with the independent function of the bladder and rectum, particularly after mesh contraction has occurred and as a result of the ongoing foreign body reaction that produces chronic inflammation. In fact, the necessary expansion and contraction of the bladder and rectum can intensify and perpetuate the inflammatory foreign body reaction to the mesh implant.[466] Moreover, to be safe and effective, the Prolift would need to maintain the expansile nature of the vagina. The vagina undergoes a limited amount of distension with filling and emptying of the adjacent organs, particularly regarding the rectum and less so with the bladder. More importantly, the vagina must be able to expand (termed “tenting” or “ballooning”) and lengthen during sexual arousal in order

[466] “Another possible explanation for the inflammatory response encountered in our study is movement of the implant. Histiocytic response to porous implants can be influenced by mechanical stress. Implants placed in mobile areas have been linked to increased infection rates and proliferation of a fibrous capsule. In fact, foreign body giant cells may be stimulated by mechanical factors alone.” PLTMEDLIT-01579: White RA et al. Histopathologic observations after short-term implantation of two porous elastomers in dogs. Biomaterials 1981; 2:171-176.

Shear forces between implant and tissue (even mechanical stretching of cells) maintains and exaggerates inflammatory reaction and foreign body capsule formation. PLTMEDLIT00118: Rosengren A, Bjursten LM. Pore size in implanted polypropylene filters is critical for tissue organization. J Biomed Mater Res Dec 2003; 67A: 918-926.

to comfortably accommodate sexual intercourse. Sexual arousal also results in vaginal wall thickening, vascular congestion, and lubrication. However, these normal aspects of vaginal function can be adversely affected as a result of Prolift mesh implantation, particularly total Prolift mesh implantation. Su et al reported impaired sexual function in women 6 months after the Prolift procedure and, in the Discussion, described that this impairment may be a result of a "condom-like effect, with the [Prolift] mesh nearly encircling the vagina,"[467] thereby preventing the normal and necessary vaginal expansion during sexual activity.

As with the hernia literature, Ethicon ignored the substantial evidence that the use of mesh, and in particular polypropylene mesh, to treat POP was not proven to be safe and effective, and instead relied on an unbalanced analysis of this literature. This literature in fact also demonstrates strong evidence of severe complications and unanswered questions.

Based on my analysis, it is my opinion that the clinical use of the Prolift device and procedure could not be justified by a thorough review of the hernia literature or preclinical testing, and that experimental clinical trials should have been performed. If such trials had taken place, it is my opinion that the risks would have been clearly shown to outweigh the benefits. This is based in part on Ethicon's own design assessments, the results of the Gynemesh PS and TVM studies, and the results of studies using the Prolift procedure.

Beginning in the mid to late 1990's, surgeons began to use certain hernia meshes off-label to augment the surgical treatment of POP. In 2002, Ethicon obtained 510(k) clearance to market Gynemesh PS mesh for use in the surgical treatment of POP. Before launch of the Prolift procedure, articles were published with regard to the use of these meshes to treat POP, including articles by the French TVM group. Ultimately, the Ethicon-sponsored French and US TVM studies were conducted, and early and limited results of those studies were used by Ethicon to justify the launch of the Prolift product and procedure.

B. Ethicon's Rationale to Support the Sale of the Prolift

Beginning in the mid to late 1990's, surgeons began to use certain hernia meshes off-label to augment the surgical treatment of POP. In 2002, Ethicon obtained 510(k) clearance to market Gynemesh PS mesh for use in the surgical treatment of POP. Before launch of the Prolift procedure, Ethicon sponsored a case series of abdominal and vaginal prolapse procedures using Gynemesh PS mesh. Data from this case series was presented in a "white paper" used by Ethicon to promote the use of Gynemesh PS mesh in prolapse repair, in abstracts, and in Ethicon marketing for Gynemesh PS mesh and, ultimately, Prolift.

Ethicon promoted the use of Gynemesh PS mesh in prolapse surgery with a "white paper" that represented early results of the case series.[468] Of a total of 161 patients, 78 cases (48%) were performed vaginally. In the patients treated vaginally, at 3 months, 8 of 59 patients

[467] Su TH, Lau HH, Huang WC, et al. Short term impact on female sexual function of pelvic floor reconstruction with the Prolift procedure. J Sex Med 2009; 6: 3201-3207.
[468] ETH.MESH.00015699

(14%) had prolapse ≥ stage II, and at 1 year, 3 of 16 patients (19%) had prolapse ≥ stage II. At 3 months, 9 of 59 patients (15%) had mesh exposure.[469] Four patients had in-office mesh excision with resolution in 2 patients and follow-up pending in 2 patients; 4 patients were treated with vaginal estrogen with follow-up pending; and 1 patient had mesh excision in the operating room with follow-up pending.

In 2004, an abstract reported results on 161 patients treated surgically with Gynemesh PS mesh, including 78 cases (48%) performed vaginally.[470] Unfortunately, the results were not presented in a way that distinguished the abdominal from the vaginal cases. Of the 161 patients, 131 patients (81%) had follow-up at 3 months, and 19 patients (14.5%) had prolapse ≥ stage II. At 1 year, 47 patients (29%) had follow-up, and 13 patients (28%) had prolapse ≥ stage II. Of the 131 patients seen at 3 months, 9 patients (7%) had mesh exposure; 4 were treated with vaginal estrogen, 4 had in-office mesh excision, and 1 had mesh excision in the operating room.

Also in 2004, a poster was presented with the same title and the same authors as the above abstract but with confusing differences in the results.[471] It is not clear how much the study population represented in this poster overlapped with that in the published abstract described above. The poster reported results on 160 patients treated surgically with Gynemesh PS mesh, including 88 cases (55%) performed vaginally. Again, the results were not presented in a way that distinguished the abdominal from the vaginal cases. At 1 year, 129 patients (81%) were seen in follow-up, and 31 patients (24%) had prolapse ≥ stage II. Mesh exposure occurred in 15 patients (11.6%),[472] and 4 patients were "managed conservatively," 8 patients had in-office mesh excision, and 3 patients had mesh excision in the operating room.

In the 2005 Prolift professional education deck, results of the Gynemesh PS mesh study were reported on 88 patients after vaginal prolapse repair. At 1 year, 14 patients (16%) had prolapse ≥ stage II. Eight patients (9.1%) had mesh exposure; 4 patients had no intervention, 2 patients had in-office mesh excision, and 1 patient had mesh excision in the operating room. Management of the remaining patient was not reported. This conflicts with data presented in the white paper and in the 2 abstracts described above. Nevertheless, Ethicon used these data to market Gynemesh PS mesh as safe and effective when used in vaginal prolapse surgery.[473] In fact, Ethicon used these data to market Prolift, "downplaying" the clinical consequences of mesh

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[469] It is not stated whether mesh exposure occurred in patients treated vaginally or abdominally; for the purposes of the frequency calculation, it is assumed that mesh exposure occurred in patients treated vaginally.

[470] Lucente V et al. A clinical assessment of GYNEMESH PS for the repair of pelvic organ prolapse [abstract]. J Pelvic Med Surg 2004; 10 (Suppl 1): S35.

[471] ETH.MESH.00411013: Lucente V et al. A clinical assessment of Gynemesh PS for the repair of pelvic organ prolapse.

[472] The abstract incorrectly calculated the frequency of mesh exposure as 9.4% (15 of 160 patients total), rather than the correct frequency of 11.6% (15 of 129 patients at 1 year).

[473] ETH-00253, Gynemesh PS mesh advertising material:
"Proven efficacy: 84% effectiveness at 1 year[4]
A multicenter, prospective study was conducted in 88 patients:
Minimal complications due to exposure
- 9% vaginal exposure rate[4]
- Only 1 patient out of 88 required operating room intervention[4]"

Cited to [4]Robinson DB. Advances in pelvic floor reconstructive surgery. As presented.

exposure by emphasizing that only 1 patient required mesh excision in the operating room.[474] Indeed, Ethicon not only downplayed the data, it failed to disclose that the patient who required operative mesh excision actually required two operations for mesh excision in the operating room.[475] Furthermore, as mentioned previously, the data conflict with the 2004 abstract described above, in which mesh exposure occurred in 15 patients at 1 year, not 8 patients, and 3 patients, not 1, required mesh excision in the operating room.[476]

Later, articles were published with regard to the use of Gynemesh PS mesh to treat POP, including articles by the French TVM group. Ultimately, the Ethicon-sponsored French and US TVM studies were conducted, and early and limited results of those studies were used by Ethicon to justify the launch of the Prolift product and procedure.

Ethicon recognized that the use of the Prolift procedure to treat POP introduced "novel morbidity" with a more severe and dangerous risk profile than traditional vaginal prolapse surgery:

> However, the use of synthetic grafts to augment pelvic floor repair and to enhance anatomic support, has created the potential for novel morbidity. Mesh exposures, visceral perforations, pelvic pain or dyspareunia are inherently possible and are associated with the implantation of synthetic grafts in the pelvic floor and needle suspension techniques, respectively.[477]

In fact, professional organizations have created entirely new classification systems for mesh-related morbidity from procedures like Prolift. For example, IUGA and ICS jointly developed a mesh-related complication classification system based on category, time, and site, with 7 areas of general description and 4 categories of clinical consequences (some of which have their own subcategories).[478] In its simplest terms, this provides at least 84 different categorizations of mesh-related morbidity. Indeed, subsequent study of the classification system found that it had poor interrater reliability, likely due in part to the large number of categories of mesh-related complications. These categories of complications never existed before permanent synthetic mesh was introduced and aggressively marketed for widespread clinical use in vaginal

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[474] ETH.MESH.02282933, draft of Prolift advertising, Heading: Demonstrated mesh safety
"In an 88-patient multicenter prospective study using Gynecare Gynemesh PS nonabsorbable Prolene Soft Mesh Implant – Only 1 patient required OR intervention†
†84% success rate at 1 year. Success defined as stage 0 to 1 prolapse. Only 3 patients required conservative office management. Four patients required no intervention."
Comment [a8]: "Medical questioned the grouping of information here in the daggered footnote. I think it works the way it is. The main purpose of this bullet was to mention that ONLY 1 PATIENTS REQUIRED OR INTERVENTION. As such we're downplaying the other information … not in an attempt to hide anything … but to keep the main bullet simple and uncluttered and unconfusing."

[475] ETH.MESH.00083242, transcript of presentation by David Robinson

[476] ETH.MESH.00411013: Lucente V et al. A clinical assessment of Gynemesh PS for the repair of pelvic organ prolapse.

[477] ETH.MESH.00596225-00596264. (See David Robinson dep., 135:15-177:8 regarding the rejection of the manuscript when submitted for publication due in large part to the bias of the Ethicon-employed authors).

[478] Haylen BT et al. An International Urogynecologic Association (IUGA) / International Continence Society (ICS) joint terminology and classification of the complications related directly to the insertion of prostheses (meshes, implants, tapes) & grafts in female pelvic floor surgery. Int Urogynecol J 2011; 22: 3-15. Epub 8-21-2010.

prolapse surgery.[479] In addition, experts have stated that the use of permanent synthetic mesh in vaginal prolapse surgery has created "a new subspecialty to manage mesh complications."[480] Note that this follows the pattern of experience after mesh implantation was introduced into hernia repair, where new categories of complications and new terms to describe them were developed in response to the mesh-related complications of hernia repair. This is yet another indication that Ethicon had every reason to anticipate the types of problems that would occur with transvaginal mesh implantation in the Prolift procedure.

Therefore, to justify the marketing of the Prolift procedure despite the knowledge and expectation that significant morbidity would be incurred, Ethicon claimed that the Prolift procedure would result in lower rates of failure and recurrent prolapse than traditional vaginal prolapse surgery. A review of the claims made in this respect, and the articles referenced, demonstrates that Ethicon did not accurately reference or summarize key articles relied on. A balanced analysis shows that Ethicon's claims of the Prolift's superiority in terms of failure and recurrent prolapse were exaggerated and misleading. Three of the articles cited often by Ethicon in sales aids, professional education decks, and PowerPoint presentations were authored by Olsen et al, Marchionni et al, and Clark et al.

Olsen et al[481]

The study population consisted of 384 women who had surgery for prolapse and/or urinary incontinence in 1995. In 112 of 384 women (29.2%), the surgery was performed for recurrent prolapse and/or urinary incontinence. An average of 12.5 years elapsed between the 1st and 2nd operations for prolapse and/or urinary incontinence.

Marchionni et al[482]

Up to 13 years after hysterectomy performed between 1983 and 1987, 448 women were examined, and 20 of 448 women (4.5%) had vaginal vault prolapse. Of the 448 women, 120

[479] Tunitsky E et al. Interrater reliability of the International Continence Society and International Urogynecological Association (ICS/IUGA) classification system for mesh-related complications. Am J Obstet Gynecol 2012; 206: 442.e1-6. Epub Mar 10 2012.

[480] Dr. Raz: "The use and abuse of mesh has created a new subspecialty to manage mesh complications. The PFD syndrome (painful, firm, and short vagina) is one of the most difficult complications to treat because, in many cases, it cannot be reversed without major surgery." Roundtable: Using mesh to repair prolapse: Averting, managing complications. Karram MM, moderator. OBG Management 2009; 21 (2): 21-28.

[481] Olsen AL et al. Epidemiology of surgically managed pelvic organ prolapse and urinary incontinence. Obstet Gynecol 1997; 89: 501-506.

[482] Marchionni M et al. True incidence of vaginal vault prolapse. Thirteen years of experience. J Reprod Med 1999; 44: 679-684.

women originally had hysterectomy for prolapse, and 8 of 120 women (6.7%) subsequently had surgery for vaginal vault prolapse.

Clark et al[483]

The study population represents the same cohort identified in the Olsen et al article, that is, 376 women identified in 1995 and followed for 5 years. Of the 264 women who had primary surgery for prolapse or stress urinary incontinence in 1995, 22 women (12% ± 4% by survival analysis) had reoperation over a 71-month time period. Of the 112 women who had repeat surgery for prolapse or stress incontinence in 1995, 15 women (17% ± 3.5% by survival analysis) had reoperation over 71 months. Reoperation at the same site was performed in 24 women (60%), at a different site in 13 women (32.5%), and at both sites in 3 women (7.5%).

These articles are inaccurately referenced by Ethicon in the following sales aids, professional education decks, and PowerPoint presentations:

2005 Prolift GPS Sales Aid:

Until now, pelvic floor repair has been highly variable with high failure rates.

- Procedures that do not take advantage of mesh implant technology have high failure rates.

-29% to 40% of all procedures fail within 3 years (Olsen, Marchionni)

-60% of recurrences are at the same site (Clark)

2005 Prolift Professional Education Deck:

Prolapse Repair – Unacceptable Failure Rates

- 29-40% of prolapse surgery is for recurrence (Olsen, Marchionni)
- 60% same site recurrence (Clark)
- 32.5% occur at different site due to unmasking of occult support defect

2007 Prolift Professional Education Deck:

How are we doing with our current surgical procedures?

- 29-40% of reconstructive procedures require surgical reintervention for failure within 3 years (Olsen, Marchionni)
- 60% of recurrences are at the same site (Clark)
- 32.5% occur at a different site due to unmasking of an occult support defect (Clark)

Pelvic Organ Prolapse Surgery slide set:[484]

How are we doing with our current surgical procedures?

[483] Clark AL et al. Epidemiologic evaluation of reoperation for surgically treated pelvic organ prolapse and urinary incontinence. Am J Obstet Gynecol 2003; 189(5): 1261-1267.

[484] Aaron Kirkemo, Medical Affairs, 1-23-2009, ETH.MESH.02217485

- 29% to 40% of prolapse surgery will be reoperation for failure within 3 years (Olsen, Marchionni).

These 3 citations in no way support the claims made. None of these articles even suggests a finding of failure within 3 years. In addition, regarding the claim of results representing "current surgical procedures," the Olsen article represented data collected in 1995 on surgery performed up to 20 years in the past, the Clark article used the same study population as the Olsen article, and the Marchionni article represented index hysterectomy performed between 1983 and 1987. Furthermore, both the Olsen and Clark articles have significant limitations in the applicability of their results, particularly as it relates to contemporary surgical practice. Data were collected at a time when hysterectomy alone was commonly performed for prolapse; therefore, the label of "reoperation" for "recurrent" prolapse is inaccurate for women who were inadequately treated at the time of their primary operation. These data also represent a time when needle suspensions were the primary form of treatment for stress incontinence; needle suspensions have since been abandoned as ineffective. Current rates of reoperation for recurrent stress incontinence are likely to be much lower since the introduction and proliferation of midurethral slings. Furthermore, data were presented regarding surgery for prolapse and/or incontinence, yet in its claims, Ethicon refers to these data as representing only surgery for prolapse.

For their own purposes in driving a perceived need for mesh use in vaginal prolapse surgery, for years, Ethicon miscited the same 3 articles selected from the medical literature and ignored the accumulating literature that reported good outcomes for traditional non-mesh vaginal prolapse surgery. Ethicon medical affairs representative Piet Hinoul was questioned in his deposition regarding Ethicon's citations to these articles and admitted that the citations from Olsen, Marchionni, and Clark were misleading. (Piet Hinoul dep., 267:10-298:3)

The inaccuracy of these claims is recognized by Dallenbach, et. al. , Incidence and risk factors for reoperation of surgically treated pelvic organ prolapse, Int. Urogynecol J. (2012) 23:35-41, pointing out that this data is misleading and overestimates the rate of reoperation for prolapse. They concluded that the risk of reoperation for recurrence of prolapse is, "between 6% and 12% rather than 30% as previously described." (41).

Claim: Knitted monofilament does not potentiate infection

The introduction of polypropylene (or any synthetic) mesh through the contaminated field of the vagina is obviously problematic. The literature unequivocally demonstrates that a mesh implant will likely become contaminated to a far greater extent when placed through the vagina than if placed abdominally.[485] Nevertheless, in both the 2005 and 2006 GPS sales aids for

[485] Contamination defined as ≥ 5000 colony-forming units (cfu) per mL. Contamination was seen in 52% (16/31) at 0.5 hour after surgical scrub; 41% (12/29) at 1.5 hours; and 25% (6/24) at 2.5 hours. Culligan P, Heit M, Blackwell L, Murphy M, Graham CA, Snyder J. Bacterial colony counts during vaginal surgery. Infect Dis Obstet Gynecol 2003; 11: 161-165. PLTMEDLIT01559.

the Prolift product, Ethicon claimed that "Knitted monofilament does not potentiate infection."[486] However, the citation does not support the advertising claim.[487] The only statement in the article regarding Prolene, not Gynemesh PS mesh, and its relation to infection is as follows: "Polypropylene mesh (Marlex, Prolene, Atrium) is a strong, non-absorbable monofilament material that is highly elastic and able to withstand infection." That the mesh itself is able to "withstand" infection is in no way equivalent to lack of potentiation of infection, particularly when placed through the contaminated surgical environment of the vagina. Ethicon miscited the information in this article to falsely reassure physicians that the synthetic Prolift mesh is not at risk for infection, even when placed through the vagina. The unsupported claim stands in direct contradiction to the warning found in the Prolift IFU indicating that one of the potential adverse reactions, among those typically associated with surgically implantable materials, is "infection potentiation…".[488] This inaccurate citation of the medical literature was also made in the Gynemesh PS marketing literature, copyright dated 2006.

Claim: Large Pore Size Fosters Proper Tissue Incorporation

In both the 2005 and 2006 GPS sales aids for the Prolift product, Ethicon claimed that "large pore size fosters proper tissue incorporation."[489] However, the citation does not support the advertising claim.[490] The study used Millipore polypropylene filters, not Gynemesh PS mesh used in the Prolift systems. The pore sizes of the studied filters were 0.6, 10, and 30 µm. The filters were implanted abdominally using sterile technique, which is a completely different surgical environment than the contaminated state of the vagina. The study did not assess "tissue incorporation" but rather focused on the inflammatory cell infiltrate and foreign body capsule that formed around the filter implants. Ethicon miscited the information in the article, depicting a clinically important event of "proper tissue incorporation" with the use of the Prolift mesh, when no such evidence was present in the cited publication. This inaccurate reference to the medical literature was also made in the Gynemesh PS marketing literature, copyright dated 2006.

Claim: Retrospective, multicenter study demonstrated improvement with few complications[491]

- 106 patients available for follow-up 3 months after surgery
- Patients had Stage III or IV prolapse
- Less than 5% failure rate, including cases of recurrent prolapse
- Mesh exposure seen in only 5 patients
  - 2 patients required surgical management of mesh exposure

[486] ETH-00291 (2006)
[487] Iglesia CB, Fenner DE Brubaker L. The use of mesh in gynecologic surgery. Int Urogynecol J 1997; 8:105-115. (PLTMEDLIT00088)
[488] ETH.MESH.02341527
[489] ETH-00291 (2006)
[490] Rosengren A, Bjurstem LM. Pore size in implanted polypropylene filters is critical for tissue organization. J Biomed Mater Res. 2003; 67A:918-926. (PLTMEDLIT00118)
[491] ETH.MESH.00161463 GPS sales aid for Prolift Pelvic Floor Repair Systems, copyright 2006

This claim is not a fair and balanced representation of the data from this citation.[492] (See below for further discussion of this article.) First, the article does not represent a study of the Prolift product and procedure; rather, it is a version of the TVM technique that had significant technical variations compared with the marketed Prolift version. Second, the article was cited incorrectly in the Prolift sales aid.[493] Third, although the article does describe the patients as having stage III and IV prolapse, staging was performed using a unique system developed by Jacquetin, described as a modification of the Baden and Walker half-way system. In the Jacquetin system, which uses 6 stages, stage III consists of prolapse 3 cm above the hymen to the hymen, and stage IV consists of prolapse up to 3 cm beyond the hymen. Therefore, stages III and IV of the Jacquetin system correspond roughly to part of stage I, stage II, and early stage III of the ICS POPQ system. Since Ethicon did not clarify this in their claim, this led doctors to believe that the patients' prolapse was more advanced than was the case.

The claim stated that the failure rate was less than 5%. However, the claim does not indicate that at least 4 patients required repeat surgery for recurrent prolapse within this extremely short duration of follow-up. In addition, at least 4 other patients required reoperation, including surgical drainage of postoperative hematomas in 2 patients and mesh excision due to exposure in 2 patients. Therefore, at least 8 patients (7.5%) required reoperation in that short time (the article did not clearly report the number of patients who required reoperation). Furthermore, other significant complications were reported in 18% of patients without stating required treatment, including 18 patients with mesh shrinkage and 1 patient with vaginal synechia (scarring). Postoperative catheterization for impaired bladder emptying was required in 6 patients for up to 73 days after the Prolift procedure.

In the conclusion of the abstract, the authors stated that "Anatomical and functional results must be assessed with a long-term follow-up to confirm the effectiveness and safety of the procedure." Ethicon did not include any statement regarding the need for long-term follow-up in its claims citing this article.

Ethicon misrepresented the balance of information contained in this article, which does not even apply to the Prolift procedure, by selectively reporting the most favorable bits of data and ignoring the remainder.

Claim: Prospective, multicenter study found perioperative complications were rare[494]

- 248 women from 25 centers received the Gynecare Prolift System

[492] ETH-02358: Fatton B, Amblard J, Debodinance P, Cosson M, Jacquetin B. Transvaginal repair of genital prolapse: preliminary results of a new tension-free vaginal mesh (Prolift™ technique) - a case series multicentric study. Int Urogynecol J 2007; 18: 743-752. Epub 11-28-2006.
[493] Fatton BF, Amblard JA, Dabadie CD, Debodinance PD, Cosson MC, Jacquetin BJ. Preliminary results of the Prolift technique in the treatment of pelvic organ prolapse by vaginal approach: a multicentric retrospective series of 110 patients. Int Urogynecol J 2006; 17: s357-360.
[494] ETH.MESH.00161463 GPS sales aid for Prolift Pelvic Floor Repair Systems, copyright 2006

- 36 patients experienced minor complications including UTI, urinary retention, and postoperative fever
- 96% of patients experienced no serious complications

Here again, Ethicon misrepresented the balance of information contained in this article.[495] Ethicon did not describe the nature of the serious complications experienced by 11 of 248 patients (4.4%), which included visceral injury in 10 cases and intraoperative hemorrhage in 1 case. The authors did not conclude that perioperative complications were rare; they concluded that perioperative serious complications were uncommon. In addition, Ethicon ignored the remainder of the authors' conclusion, which stated that "particular care should be taken to detect visceral injury at the time of surgery." Neither the original Prolift IFU nor the Prolift surgical technique document contained any recommendations about detecting visceral injury at the time of Prolift surgery, such as by performing cystoscopy and digital rectal examination.

Furthermore, in the Discussion section of the article, the authors expressed concern about the risk for adverse reactions and mesh-related complications because of the greatly increased size of the Prolift mesh, compared with the mesh load from suburethral sling surgery. The authors stated that "Caution is advised until large-scale long-term prospective safety studies describing biocompatibility are available." Ethicon represented none of this concern or caution in citing this article to support its marketing claims.

Claim: Multicenter case study demonstrated a return of sexual function after surgery[496]

- 89 patients
- Stage III or IV prolapse
- Failures (6 total) were Stage II or less
- Mean follow-up: 5 months
- Incidence of sexual function
  - 6/49 previously inactive patients became sexually active postoperatively
  - 7/40 patients who were active before surgery did not resume sexual activity
- 95% of sexually active patients experienced no negative impact on sexual activity

Ethicon used this citation to claim a "return" of sexual function after surgery.[497] As with the Fatton et al citation above, this abstract does not represent the Prolift procedure, but rather the US TVM study. (See below for further discussion of the TVM studies.) Although Ethicon claimed that this study included only patients with stage III and IV prolapse, the abstract

[495] ETH-02277: Altman D, Falconer C for the Nordic Transvaginal Mesh Group. Perioperative morbidity using transvaginal mesh in pelvic organ prolapse repair. Obstet Gynecol 2007; 109: 303-308.
[496] ETH.MESH.00161463 GPS sales aid for Prolift Pelvic Floor Repair Systems, copyright 2006
[497] Murphy M, Raders JL, Haff R, Yeager M, Lucente VR. Early US experience with vaginal extraperitoneal colpopexy using a polypropylene graft (Prolift) for the treatment of pelvic organ prolapse. J Pelvic Med Surg 2006; 12: 104-105 [abstract].

indicated that 1 patient had stage I prolapse, and 19 patients had stage II prolapse; therefore, nearly one-quarter of the patients (20 of 89, 22%) had early prolapse. The abstract did not provide data on primary versus recurrent prolapse. Ethicon misstated the duration of follow-up; patients were seen for office examination at a median of 3 months after surgery, and a telephone survey was performed at a median (not mean) of 5 months after surgery. As Ethicon claimed, the abstract reported that 6 of 49 patients (12%) who were not sexually active before surgery became sexually active after the surgery; however, Ethicon misstated the number of previously sexually active patients who had not resumed sexual activity as 7 instead of 8 patients (8 of 40, 20%). Finally, Ethicon's claim that 95% of sexually active patients had no negative impact on sexual activity has no basis in fact from the abstract. Patients' preoperative sexual function was evidently not measured; the abstract reported that 32 of the 38 women who were sexually active after surgery completed a questionnaire to assess sexual function (PISQ-12). The average score of 103.8 ± 10.1 was considered comparable to historical controls without prolapse.

The above series of misstatements and selective reporting to support marketing claims are typical of Ethicon's misrepresentations from the medical literature and in no way reflect a fair and balanced portrayal of the risks and benefits of the Prolift Systems. Although many Ethicon employees gave deposition testimony that Ethicon provided fair and balanced information in its marketing of the Prolift product and procedure to physicians and patients, the evidence discussed above clearly contradicts that.

Outcomes of Vaginal Prolapse Surgery

In clinical studies, staging of pelvic organ prolapse is typically performed using the Pelvic Organ Prolapse Quantification system (POP-Q; also known as ICS [International Continence Society] prolapse stage). The overall stage of prolapse is determined by maximal prolapse affecting the vaginal apex or cervix, anterior vagina, or posterior vagina.[498] In the NIH terminology document that defined outcomes after prolapse surgery, optimal anatomic outcome was defined as ICS Stage 0, satisfactory anatomic outcome was defined as ICS Stage I, and unsatisfactory anatomic outcome was defined as ICS Stage II or greater, or no change or worsening from pretreatment position.[499] However, the POPQ system of staging prolapse has several important limitations. For example, all sites in the vagina are categorized by the same staging criteria, but stage II apical or uterine prolapse represents a much greater degree of prolapse than stage II anterior or posterior vaginal prolapse. When the vaginal apex or cervix has prolapsed enough to be categorized as stage II (for example, -1 cm), that represents prolapse approximately equal to the length of the vagina (typically, 8-12 cm). In contrast, to reach stage II

[498] PLTMEDLIT00872: Bump RC et al. The standardization of terminology of female pelvic organ prolapse and pelvic floor dysfunction. Am J Obstet Gynecol 1996; 175:10-17. Stage 0: position of the vaginal apex or cervix within 2 cm of total vaginal length; position of the anterior and posterior vagina without prolapse; Stage I: position of the vagina more than 1 cm above the hymen but lower than Stage 0; Stage II: position of the vagina between 1 cm above and 1 cm beyond the hymen; Stage III: position of the vagina more than 1 cm beyond the hymen but within 2 cm of total vaginal length; Stage IV: position of the vagina beyond the hymen to the extent of total vaginal length.
[499] PLTMEDLIT00103: Weber AM et al. The standardization of terminology for researchers in female pelvic floor disorders. Int Urogynecol J 2001; 12: 178-186.

anterior or posterior vaginal prolapse only requires prolapse of 2 cm (no prolapse at -3 cm, stage II prolapse from -1 cm to +1 cm).

In addition, the POPQ system is affected by patient-related conditions such as bladder fullness,[500] it has a significant subjective component, and it is susceptible to bias. The extent of prolapse is intended to be measured at maximal Valsalva effort (bearing down or "pushing"). However, what constitutes "maximal" effort is an entirely subjective component. Indeed, this subjective component of the POPQ system may explain, at least in part, the finding that substantial differences in POPQ assessment occur depending on whether the measurements were made by the operating surgeon or by an independent observer.[501]

Furthermore, an amount of variation inherent in the measurements themselves (imprecision) can lead to a stage change that has no or questionable clinical significance for the patient. For example, by the NIH criteria, anterior vaginal prolapse at -2 cm (stage I) is categorized as a "success." Yet, a change of only 1 cm, to -1 cm (stage II), is categorized as a "failure." Such is the nature of arbitrary thresholds, inherent and possibly unavoidable in definitions such as these.

It is important to keep all these limitations of the POPQ system in mind when interpreting the results of studies that rely on anatomic outcomes as their primary measure of effectiveness. Even more important to defining the "success" or "failure" of prolapse surgery is the patients' experience of the outcomes. This is discussed in more detail below.

Since publication of the NIH criteria, studies of prolapse surgery have commonly defined anatomic outcomes of stage 0 or I as "cure" or "success" and stage II and greater as "failure" or "recurrent prolapse." However, in the Discussion section of the article that set forth these criteria of success and failure after prolapse surgery, the authors pointed out the clear limitations of these definitions of cure and failure:

> The definitions of prolapse presented here are based on findings at physical examination. Any current distinction between 'normal' physical examination findings and 'abnormal' findings that constitute prolapse is arbitrary, as data correlating symptoms to physical findings is lacking. … In addition, we recognize that many women who may be categorized as 'anatomic failures' are, in fact, satisfied with their postsurgical results; we anticipate that evidence provided by further research will allow

[500] Haya N et al. The effect of bladder fullness on evaluation of pelvic organ prolapse. Int J Urogynaecol Obstet 2012 Apr 14; Epub ahead of print. After bladder filling to maximum cystometric capacity, prolapse was underestimated by a full stage (median, stage II with full bladder versus stage III with empty bladder). Maximal prolapse of the anterior vagina was most strongly affected.

[501] Antosh DD et al. Outcome assessment with blinded versus unblended POP-Q exams. Am J Obstet Gynecol 2011; 205: 489.e1-4. Epub July 20, 2011. Overall prolapse recurrence was 15% higher when assessed by an independent observer than by the operating surgeon.

subsequent refinement of these definitions to take into account the relief of symptoms and patient satisfaction, as well as anatomic outcomes.

Unfortunately, these limitations still exist and explain the paradoxical findings of many studies that have reported seemingly high rates of "failure" paired with good subjective outcomes, high patient satisfaction, and low rates of reoperation for recurrent prolapse. In fact, this paradox lies behind a series of articles that emphasize the lack of full understanding of what constitutes successful prolapse surgery, when improvement of quality of life is the primary purpose of the surgery.

Weber et al published a randomized trial of anterior colporrhaphy techniques.[502] Using the NIH criteria, cure was defined as ICS Stage 0 or I in the anterior vaginal position. At median follow-up of 23.3 months, cure was obtained in 30% of standard anterior colporrhaphy, 42% of standard anterior colporrhaphy with overlay of polyglactin mesh, and 46% of ultralateral (modified) anterior colporrhaphy. Because of these results, this article has been widely cited as establishing the need for a better repair than traditional colporrhaphy. However, the severity of prolapse symptoms, measured on 10-point visual analog scale, decreased from 6.9 ± 2.7 preoperatively to 1.1 ± 0.8 postoperatively. In the Discussion section of the article, the authors interpreted the apparent contradiction between the high rates of anatomic "failure" with very low levels of prolapse symptoms: "… the low rate of symptoms in these patients [with the anterior vagina at the level of the hymen] shows that many patients are satisfied with their surgical results. … It is possible that strict definitions of anterior vaginal wall measurements may be poor predictors of 'success' with this particular operation [anterior colporrhaphy]."

As with outcomes after surgery for stress incontinence, outcomes after surgery for prolapse vary tremendously depending on the definitions used. Anatomic outcomes had traditionally been the basis for reporting results after prolapse surgery, as in the Weber et al trial, in part due to the absence of validated questionnaires to assess subjective outcomes such as symptom burden, condition-specific health-related quality of life, and sexual function.[503] Fortunately, that has now changed, and critically important subjective outcomes can now be assessed with validated tools. It cannot be emphasized strongly enough that, since prolapse is a condition that only affects quality of life (as opposed to quality AND quantity of life, as in cancer and heart disease), the definition of successful treatment should rely most heavily on improved quality of life as experienced by the patient. This is as logical as it is obvious. It has

[502] ETH-76591: Weber AM et al. Anterior colporrhaphy: a randomized trial of three surgical techniques. Am J Obstet Gynecol 2001; 185: 1299-1306.

[503] Barber MD et al. Psychometric evaluation of 2 comprehensive condition-specific quality of life instruments for women with pelvic floor disorders. Am J Obstet Gynecol 2001; 185: 1388-1395.
Barber MD, Walters MD, Bump RC. Short forms of two condition-specific quality-of-life questionnaires for women with pelvic floor disorders (PFDI-20 and PFIQ-7). Am J Obstet Gynecol 2005; 193: 103-113. (PLTMEDLIT-00001)
Rogers RG et al. A new instrument to measure sexual function in women with urinary incontinence or pelvic organ prolapse. Am J Obstet Gynecol 2001; 184: 552-558.
Rogers RG et al. A short form of the Pelvic Organ Prolapse/Urinary Incontinence Sexual Questionnaire (PISQ-12). Int Urogynecol J 2003; 14: 164-168.

also been clearly demonstrated in a study that compared 18 different definitions of success after prolapse surgery and found subjective cure of prolapse was strongly associated with the patients' assessment of treatment success and overall improvement, more so than any other definition tested.[504] In addition, a recent review emphasized that the most important factor in defining cure of prolapse should be patient symptoms.[505]

Of interest, data from the Weber et al trial were recently reanalyzed using clinically relevant definitions of success.[506] Success was defined as no prolapse beyond the hymen, visual analog scale (VAS) ≤ 2 for prolapse symptoms, and no retreatment. Overall, 66 of 75 patients (88%) had successful treatment at 1 year; 67 of 75 patients (89%) had no prolapse beyond the hymen, and 80 of 84 patients (95%) had VAS ≤ 2 for prolapse symptoms. Only 1 of 113 women (1%) had surgery for recurrent prolapse 29 months after index surgery. No reoperations were necessary for complications. By time-to-event analysis, overall treatment success at 30 months was 81.5%.

This important distinction between anatomic and subjective outcomes in assessing the result of prolapse surgery has been recognized by professional organizations in response to the growing concern about mesh-related complications. For example, the ACOG/AUGS committee opinion on Vaginal Placement of Synthetic Mesh for Pelvic Organ Prolapse stated that "Native tissue repair may have better success rates than previously thought."[507] The committee opinion discussed the original and reanalyzed data from the Weber et al trial, stating that "Previous studies used definitions of success that may have been too stringent" and that "subjective patient-oriented success and quality of life outcomes need to be considered as well."

D. The TVM Technique and Prolift

David Robinson testified that the support relied on by Ethicon to establish the safety and effectiveness of the Prolift procedure and to support the launch of the Prolift procedure was the early and limited results of the French and US TVM studies, a representative study by physicians in the French TVM group, and the Gynemesh PS data. (David Robinson dep., 87:7-88:9; 111:17-21). The French TVM group published the results of their ongoing development of the TVM procedure during the years before the Ethicon-sponsored TVM studies were completed. The results of these studies provided very concerning data.

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[504] Barber MD et al. Defining success after surgery for pelvic organ prolapse. Obstet Gynecol 2009; 114: 600-609. Subjective cure was defined as a negative response to 2 questions from the Pelvic Floor Distress Inventory: 1) Do you usually have a sensation of bulging or protruding from the vaginal area? 2) Do you usually have a bulge or something falling out that you can see or feel in the vaginal area?

[505] Lee U, Raz S. Emerging concepts for pelvic organ prolapse surgery: what is cure? Curr Urol Rep 2011; 12: 62-67.

[506] PLTMEDLIT01963: Chmielewski L et al. Reanalysis of a randomized trial of 3 techniques of anterior colporrhaphy using clinically relevant definitions of success. Am J Obstet Gynecol 2011; 205: 69.e1-8.

[507] Vaginal placement of synthetic mesh for pelvic organ prolapse. Committee Opinion No. 513. American College of Obstetricians and Gynecologists. Obstet Gynecol 2011; 118: 1459-1464.

2004, Berrocal et al[508]

One of the first articles summarized the early work of the TVM Group, beginning on June 5, 2000, supported by Gynecare France.[509] The article discussed the TVM technique protocol and the fact that the technique had been developed and changed through cadaver trials and a feasibility phase. In commenting on prior literature with regard to patient selection criteria, the article stated that the "… authors [Iglesia et al] still do not recommend their use [mesh] for primary repair [of prolapse] because of reported complications," including erosion, prosthetics ablation, formation of a sinus trajectory [tract], and urethral erosion.[510] In discussing the requirements of mesh material used in vaginal prolapse surgery, the article stated that "The concept of interstice[s] must be clearly understood [because] of the risk of infection associated with endovaginal surgery. Porosity is also a major mesh characteristic. Porosity will promote colonization of the prosthetic tissue 'like a lattice by ivy.' … An estimated 75-µm threshold is required to obtain adequate tissue integration. …" However, the 75-µm threshold was established with regard to abdominal hernia repair,[511] not vaginal prolapse repair, and Ethicon knew that the pore sizes needed to be at least 1000 um in all directions to be sufficient. The Kirsten Spychaj presentation from February 23, 2007 states the need for 1000 um pores clearly.[512][513] The Muhl article presents textile porosity and size of the largest pore spaces for several commercially available meshes. It is important to note findings by Klinge et al regarding the difference between textile porosity *ex vivo* and effective porosity *in vivo*, with effective porosity always being lower than textile porosity.[514] The distance between the mesh fibers is the open spaces known as pores. If the distance between the mesh fibers is less than 1 mm in all directions once implanted and subject to the in vivo forces of the female pelvis, the mesh will not have sufficient effective porosity to prevent fibrotic bridging, which is one of the causes of mesh contraction.[515]

Indeed, these authors stated that "**The retraction phenomenon is impossible to forecast and highly variable.**" Although the authors stated that "this phenomenon appears enhanced with one-thread [monofilament] materials," they nevertheless chose a monofilament mesh to be used

[508] Berrocal J et al. Conceptual advances in the surgical management of genital prolapse: The TVM technique emergence. J. Gynecol Obstet Biol Reprod 2004; 33: 577-587. (ETH-02800)
[509] Berrocal J et al. Conceptual advances in the surgical management of genital prolapse: The TVM technique emergence. J. Gynecol Obstet Biol Reprod 2004; 33: 577-587. (ETH-02800) "The firm Gynecare France is in charge of the logistic and material coordination of the group."
[510] Iglesia CB et al. The use of mesh in gynecologic surgery. Int Urogynecol J 1997; 8: 105-15; erosion in 10% of cases with ePTFE [polytetrafluoroethylene], prosthetics ablation in up to 35% and formation of a sinus trajectory in 10% with Gore-Tex, and urethral erosion in 4% with Marlex.
[511] Amid PK. Classification of biomaterials and their related complications in abdominal wall hernia surgery. Hernia 1997; 1:15-21. PLTMEDLIT00681
[512] ETH.MESH.02092787.
[513] Muhl, et al. New Objective Measurement to Characterize the Porosity of Textile Implants. J. Biomed Mater Res Part B: Appl Biomater 84B:176-183, 2008 (ETH.MESH.02184131).
[514] Klinge U, Klosterhalfen B. Modified classification of surgical meshes for hernia repair based on the analyses of 1,000 explanted meshes. Hernia DOI 10.1007/s10029-012-0913-6
[515] Klinge U, Klosterhalfen B. Modified classification of surgical meshes for hernia repair based on the analyses of 1,000 explanted meshes. Hernia DOI 10.1007/s10029-012-0913-6

in the TVM procedure. The chosen material was Gynemesh Soft, described as "a low weight (42.7 g/m[1] [sic]), thin (0.42 mm) and high porosity (64%) synthetic, one-thread polypropylene prosthesis." The TVM technique was described in detail; the steps of dissection and mesh implantation resembled what became the Prolift procedure except for the inserter tools. However, the mesh implant itself differed from the Prolift mesh implant, particularly in the relation between the mesh arms and mesh body. In addition, the surgical technique differed from the Prolift procedure, especially regarding placement of the skin incisions through which the mesh arms were passed, thereby affecting the final location of the mesh itself. After anterior mesh placement, the authors described that "the prosthesis can be tensed; adjustment is not difficult since the prosthesis surface [area] has been calculated to remain relatively free under the bladder while ensuring lateral contact against the ATFP [arcus tendineus fasciae pelvis]." Therefore, the authors, the inventors of the TVM technique, gave no objective or quantifiable means of placing the mesh in a "tension-free" manner. To this day, Ethicon has never addressed this critically important flaw in the fundamental underpinning of the TVM technique that is now the Prolift procedure.

The article reported that "Our review of the relevant literature has been relatively disappointing," in terms of the number of previous reports of mesh use in vaginal prolapse surgery. With regard to complications, the article stated that "Although the relatively easy to treat erosion phenomenon is often reported in these studies, none mentions the much more worrying retraction phenomenon and its after-effects, the symptomatic manifestation of which is dyspareunia." However, the authors themselves do not describe their experience with mesh retraction, beyond stating that it is highly variable and impossible to predict; neither do the authors describe how to prevent it or how to manage it once it has occurred. After describing technique modifications that reduced the erosion rate, they speculate that the use of Prolene Soft "might have a beneficial effect on retraction events, but this warrants further confirmation."

The conclusion states in part that "This technique should be reserved for the management of Grade 3 and 4 prolapse, possibly as first-line treatment. The intervention lasts no more than 120 minutes and can be performed following a short training period, by any surgeon interested in pelvic floor surgery and with experience in the vaginal route." This statement, that any surgeon experienced with vaginal prolapse surgery can perform the TVM procedure, is in direct contradiction to feedback obtained during initial training for the Ethicon TVM studies and Ethicon's stated intent to limit training on the Prolift procedure to high-volume, experienced surgeons. (Paul Parisi dep., 781:5-15). In addition, the authors state that "The reasoning followed by the TVM group led to the initiation of a study that will analyze the long term results." However, the authors do not define what constitutes "long term" results, especially given the newness of the procedure and the permanence of a large body of mesh placed vaginally.

2005, Collinet et al.[516]

[516] Collinet et al. Transvaginal mesh technique for pelvic organ prolapse repair: mesh exposure management and risk factors. Int Urogynecol J 2006 Jun; 17: 315-320. Epub 10-15-2005. (ETH-02794)

This article described mesh exposure in 277 patients who underwent POP surgery via the TVM technique[517] with either Prolene mesh (39%) or Prolene Soft mesh (61%) in a retrospective study between January 2002 and December 2003. Mesh exposure was seen in 34 patients (12.27%) at 2 months, with 25 of 34 patients (74%) requiring partial mesh excision. No difference was seen in mesh exposure with the Prolene and Prolene Soft meshes. A second mesh excision was required in 2 of the 25 patients (8%), and 1 patient required a third mesh excision (4%). One patient developed a vesicovaginal fistula after mesh excision and required surgical repair.

In the introduction, the authors state, in part, "Unfortunately, because of secondary complications associated with the vaginal mesh approach, this new method is not entirely satisfactory." They distinguish between mesh exposure, which they attribute to "inadequate healing," and "infected mesh material" that requires "complete and rapid removal of the material in order to prevent serious surgical sequelae." In addition, the authors distinguish between "delayed healing" with mesh exposure that (apparently) responds to vaginal estrogen or antibiotics, and "absence of healing" with mesh exposure that requires partial mesh excision. In this retrospective study using only univariable analysis, risk factors for mesh exposure included concomitant hysterectomy and inverted T-colpotomy. That no difference was seen in mesh exposure with Prolene or Prolene Soft belied Ethicon's expectations that Prolene Soft mesh (the same as Gynemesh PS mesh) would have fewer complications than Prolene mesh when used in vaginal prolapse surgery.[518] To minimize the occurrence of mesh exposure, the authors recommended that the "uterus must be preserved, and the number and extent of vaginal incisions needed to insert the mesh must be limited."

In the conclusion of the article, published months after the Prolift procedure was first marketed, the inventors of the TVM procedure emphasized that:

> … based on these data, we can only advise that caution be exercised when carrying out this new surgical procedure. In fact, experimental studies and clinical trials seem necessary in order to reduce the level of exposure to less than 5% of cases…. Moreover, long-term follow-up is needed in the event of complications arising from mesh implantation.

Ethicon ignored these recommendations and never performed experimental studies or clinical trials of the Prolift procedure to understand the etiology of mesh exposure or to develop effective methods of prevention and management. Moreover, Ethicon ultimately introduced the

[517] However, in Figure 3 that depicts the mesh implant used with the TVM technique, the Prolift mesh implant is depicted, rather than the TVM mesh implant. (ETH-02796)

[518] This was also demonstrated in a subsequent study, when mesh erosion occurred even more frequently with the use of Gynemesh PS mesh (24%) than with Gynemesh mesh (16%). Deffieux X et al. Vaginal mesh erosion after transvaginal repair of cystocele using Gynemesh or Gynemesh-Soft in 138 women: a comparative study. Int Urogynecol J 2007 Jan; 18: (1): 73-79. Epub 2006 Jan 4. ETH-02955

Prolift + M product with Gynemesh M mesh (Ultrapro) in an effort to decrease complications, including mesh exposure, that occurred so commonly with Prolift.

2005, Abstract, Cosson et al[519]
2008, Article, Caquant et al[520]

Per an Ethicon Product Pointer,[521] this abstract was presented by Prof. Cosson on September 2, 2005, at which time he clarified that the study did not use the Prolift product (despite the abstract's title) since the study began in 2002, before Prolift was available. Although the abstract was presented in 2005, the article representing these data was not published until 3 years later; the data were not updated to reflect any further follow-up in the intervening 3 years. The study included 684 patients with a mean of 3.6 months (range, 2-18 months) follow-up after Gynemesh PS mesh implantation using the TVM technique.[522] Prolapse recurred in 36 patients (5.3%). Prolapse recurrence was not defined, and the number of patients who required subsequent surgery for recurrent prolapse was not stated. In the abstract, the authors expressed their disappointment at this high rate of prolapse recurrence with such short follow-up: "… More worrying are high rates of OPR [organ prolapse recurrence], all the more so as follow-up is rather short (mean of 3.6 months). … high rates of organ prolapse recurrence at only 3.6 months make us wonder what long-term anatomical results would be."

New development of stress urinary incontinence occurred in 37 patients (5.4%). The number of patients who required subsequent surgery for stress incontinence was not stated. Although the authors stated that this study confirmed "short-term safety," complications occurred in 26.7% of the patients, including mesh shrinkage in 11.7%, vaginal mesh exposure in 11.3%, and serious intraoperative and postoperative complications in 3.7% (hematoma, organ injury, severe pelvic infections, rectovaginal and vesicovaginal fistulas). In addition, 75 patients (11%) required reoperation, a matter of grave concern given the extremely short follow-up period. In addition, reoperation for recurrent prolapse and new stress urinary incontinence was not stated; therefore, the true frequency of reoperation was underestimated in this study.

The authors also noted that "Large variations between centers in incidences of medium-term post-operative complications are noticed." This is particularly concerning coming from the inventors of the TVM technique. It can only be assumed that variation in outcomes would be even higher for the TVM technique and the Prolift procedure when introduced to a larger segment of the surgeon pool, who by definition are more inexperienced with the technique since it differed so markedly from traditional vaginal prolapse surgery. In addition, this finding of

[519] ETH-02351: Cosson M et al. Prolift mesh (Gynecare) for pelvic organ prolapse surgical treatment using the TVM group technique: a retrospective study of 687 patients. ICS Abstract 121, 9-2-2005
[520] PLTMEDLIT01656: Caquant F et al. Safety of Trans Vaginal Mesh procedure: Retrospective study of 684 patients. J Obstet Gynecol Res 2008; 34 (4): 449-456. Journal impact factor = 0.869 (for comparison, journal impact factor of Obstetrics & Gynecology = 4.392).
[521] ETH.MESH.02347160
[522] Again, as in the previously discussed article, in Figure 1 that depicts the mesh implant used with the TVM technique, the Prolift mesh implant is depicted, rather than the TVM mesh implant. PLTMEDLIT01657

large variation in outcomes among the inventors belies an earlier statement from the TVM group that "any surgeon can apply this technique after a short period of training."[523]

2005, Abstract, Cosson et al[524]

Per an Ethicon Product Pointer,[525] Abstract 686 represents a subset of 96 patients of less than 50 years of age from the 684 patients presented in Abstract 121 (see above). Although the authors stated that this study confirmed the TVM procedure's "safety for women of less than 50 years old," 18% of women experienced complications including intraoperative organ injury and hemorrhage, hematomas and abscess formation, and surgical treatment for granulomas, mesh exposure, and mesh retraction.[526] An additional 11% of women developed recurrent prolapse and new stress incontinence.[527] Again, the authors noted "large variations between centers in incidences of medium-term post-operative complications." The authors recommend assessing the durability of anatomical results over a longer period, but they describe medium-term outcomes as "more disappointing" due to high rates of granuloma formation, vaginal mesh exposure, and recurrent prolapse.

2005, Miller et al[528]

Per an Ethicon Product Pointer,[529] this video abstract was presented by Dr. Miller at ICS, with regard to early data from the French and US TVM studies. The Product Pointer stated that since the data changed after abstract submission due to the data clean-up process, "**THE RESULTS ARE PRELIMINARY, INCOMPLETE AND UNVERIFIED**." The abstract claimed that peri-operative safety results of the TVM technique were "favorable," and complication rates were "consistent with other POP repairs (both mesh and non-mesh)." However, based on the data presented, 18 of 180 women (10%) incurred serious intraoperative and early postoperative complications, including hematoma, abscess formation, hemorrhage, rectal injury, ureteral injury, ureteral stricture, urinary retention, and rectovaginal and vesicovaginal fistulas. By way of comparison as to the frequency of complications with traditional vaginal prolapse surgery, in the Altman et al trial, only 1 of 189 women (0.5%) in the anterior colporrhaphy group had an intraoperative complication, which was a bladder injury; no patients had hematoma, abscess formation, hemorrhage, rectal or ureteral injury, or fistula formation, and no patients required reoperation for an intraoperative or postoperative

[523] ETH-02801, Berrocal J et al. Conceptual advances in the surgical management of genital prolapse: The TVM technique emergence. J. Gynecol Obstet Biol Reprod 2004; 33: 577-587.
[524] ETH.02354: Cosson M et al. Prolift mesh (Gynecare) for pelvic organ prolapse surgical treatment using the TVM Group technique: A retrospective study of 96 women of less than 50 years old. ICS Abstract 686, 9-2-2005
[525] ETH.MESH.02347161
[526] The total number of women who developed granulomas, mesh exposure, and mesh retraction was not provided, only the number that required surgical treatment.
[527] Need for treatment for recurrent prolapse and new stress incontinence was not provided.
[528] ETH.MESH.00482987: Miller D et al. Trans-Vaginal Mesh (TVM): An Innovative Approach to Placing Synthetic Mesh Transvaginally for Surgical Correction of Pelvic Support Defects – Peri-operative Safety Results. ICS/IUGA Abstract 406, August 2005.
[529] ETH.MESH.02347163

complication.[530] As discussed in further detail in other sections of this report, complication rates during and after the TVM technique are emphatically NOT consistent with complications of traditional vaginal prolapse surgery.

The authors stated that "Long-term follow-up evaluations are ongoing to provide more insight into post-operative complications as well as the effectiveness of the TVM technique." It is important to emphasize that complications after traditional vaginal prolapse surgery occur only in the intraoperative and immediate postoperative period, in stark contrast to the life-long risk of serious complications after mesh surgery. Given the high rate of immediate and early complications and the certain addition of later postoperative complications due to the life-long risk of mesh-related complications, the risks of the TVM technique that became the Prolift procedure greatly outweigh the benefit, if indeed there is a benefit over traditional prolapse surgery.

The data in this abstract represented 180 women in the French and US TVM studies. However, the data from 5 women were supposed to be removed from the analyses, because these patients had been enrolled before IRB approval of the study protocol at the investigational site.[531] Nevertheless, here and elsewhere, Ethicon permitted these data to be presented anyway, in an unacceptable breach of ethical standards under which clinical research should be performed.

2006, French TVM study[532] (1-year report: June 27, 2006)

This study, an open-label observational cohort without a control group, enrolled 90 patients from 8 sites in France and reported 12-month follow-up on 87 patients. Gynemesh PS mesh was provided by Ethicon and cut by the surgeons using a template into a shape resembling but not identical to that of the Prolift mesh implant. Although the surgeons were expected to cut the implant to the provided template, it later became evident that not all surgeons were adhering to this requirement and instead were hand-cutting the mesh implant without following the template.[533] Ethicon had no plans in the study protocol as to how to handle this protocol deviation; as late as January 2006, well after all study participants had been enrolled and at the time when 1-year follow-up was close to completion, Ethicon staff were still confused as to whether the data from these patients were to be included or excluded in the final analysis.[534] As discussed in more detail below, this is another example of Ethicon's appallingly poor planning

[530] Altman D, Vayrynen T, Engh ME et al (2011) Anterior colporrhaphy versus transvaginal mesh for pelvic-organ prolapse. N Engl J Med 364(19):1826–1836.
[531] ETH.MESH.00401483
[532] ETH-01074-01154 Clinical Study Report Protocol Number CT-TVM-001-03 with 1-year follow-up.
[533] ETH.MESH.00401457, Email 1-31-2006 about protocol violations, from Allie Smith: "On the French study some material was hand cut …"
[534] ETH.MESH.00401457, Emails 1-31-2006 about protocol violations, from Allie Smith: "On the French study some material was hand cut, I know that there were discussions about analysis i.e. including and excluding these patients but I can't remember what was decided. …"
Response from Pete Jones: "Regarding the hand cut material, I thought this was included as a PV [protocol violation], but we decided the PVs (except one) were not major, hence we would not do a per-protocol set. …"

and mismanagement of critically important aspects of the TVM study's design and implementation.

The mesh implant was placed using the TVM technique with a needle threaded with suture, and the suture was then used to pull the mesh arms through the tissue. This is distinctly different than the Prolift procedure, in which a cannula-equipped guide is used to create tissue channels through which the mesh arms are passed using a retrieval device, leading to roping and curling of the arms. Other important differences in surgical technique between the TVM and Prolift procedures include location of the skin incisions for the introduction for the superficial anterior, deep anterior, and posterior cannula-equipped guides, which ultimately affects exactly where the mesh is implanted.

Although the study protocol required that patients have preoperative prolapse ≥ ICS stage III, 14 of 90 patients (16.3%) had stage II prolapse at baseline. The protocol required that patients have previous or concomitant hysterectomy and that the index surgery used a total mesh implant (intact or cut into anterior and posterior pieces). The 12-month report defined failure of prolapse ≥ stage II when the upper bound of a 90% two-tailed confidence interval (CI) exceeded 20%.[535]

The 12-month report stated that failure occurred in 16 of 87 patients (18.4%). However, the data tables identified 18 of 87 patients (20.7%) with ≥ stage II prolapse at 1-year follow-up, including 2 patients who required reoperation for recurrent prolapse.[536] Since the upper tail of the 90% confidence interval exceeded 20% (26.6%), this did not meet the predetermined criterion for success. As with preceding work from the TVM group,[537] and despite the fact that the TVM procedures were performed by the TVM group that invented the technique over a period of years, large differences in failure occurred at different sites, varying from 0% to 50%.[538] Neither the TVM group nor Ethicon apparently ever investigated why such a high degree of variation was seen between centers. Given these differences were seen with the surgeons who invented the TVM technique, it can only be assumed that even more variability in outcomes (lower success, higher complications) would occur when the TVM technique and Prolift procedure were performed by less experienced surgeons.

Intraoperative adverse events occurred in 5 of 90 patients (5.6%), including hemorrhage in 2 patients and 1 patient each with rectal perforation, vaginal perforation, and urinary retention; this frequency of intraoperative adverse events was described as "low" in the report's safety conclusions.[539] By comparison, systematic reviews of traditional vaginal prolapse surgery have reported intraoperative complications of 1.0% with uterosacral ligament suspension and other

[535] ETH-01077
[536] ETH-75916
[537] ETH-02351, ETH-02354, PLTMEDLIT01656
[538] ETH-01117
[539] ETH-01134

prolapse and/or incontinence procedures, and 0.8% with sacrospinous ligament fixation and other prolapse and/or incontinence procedures.[540]

However, the French TVM report's safety conclusions did not consider the high frequency of postoperative adverse events in its conclusions, particularly the very high reoperation rate. A total of 22 operations in 20 patients (20 of 87, 23%) were necessary in the 12 months after the index surgery, including 5 mesh excision procedures in 4 patients, 1 vesicovaginal fistula repair with ureteral reimplantation (2 operations), sling procedures for stress incontinence in 9 patients, 1 sling section after TVT-O, recurrent prolapse repair in 2 patients, 1 vaginal adhesion section, and 3 other reoperations.[541] A total of 131 adverse events occurred in 90 patients, with 68 patients (76%) experiencing 1 or more adverse events. Serious adverse events occurred in 22 patients (24%), and severe adverse events occurred in 9 patients (10%). Of the 90 patients, 45 patients (50%) required treatment for adverse events.[542]

Moderate or severe vaginal retraction was reported in 11 of 87 patients (12.6%). Vaginal mesh exposure occurred in 9 of 87 patients (10.3%). Palpable vaginal mesh was also described, but the investigators themselves questioned whether the definition of palpable mesh was consistently applied.[543]

The number of sexually active patients dropped substantially after surgery, from 61 patients at baseline to 40 patients at 12 months (a 33% decrease), implying that the TVM procedure interfered with resumption of sexual activity in ways that were not measured. The 12-month report stated that new dyspareunia occurred in 7 patients (8%) at 6 months and in 3 patients (3.4%) at 12 months, but in the way the data were presented, it was not possible to determine whether the number of patients experiencing new dyspareunia at 12 months was a total of 10 patients (10 of 40, 25%) or some other number.[544]

The French TVM study had a number of serious limitations, including a disturbingly high frequency of inaccurate measurements of prolapse status using the POPQ system. For example, one table based on data analysis in May 2006 contained 62 entries that were incompatible with the definitions of the POPQ staging system.[545] Considering that the POPQ measurements defined the primary study endpoint of success or failure, this markedly high frequency of errors introduces doubt as to whether the study results can be trusted. The study was already deemed a failure by > 20% of patients with ≥ stage II prolapse at 1 year. The interim data at 6 months,

[540] PLTMEDLIT00012: Marguiles RU et al. Outcomes of transvaginal uterosacral ligament suspension: systematic review and meta-analysis. Am J Obstet Gynecol 2010; 202: 124-134. Intraoperative complications occurred in 8 of 820 patients, including ureteral injury requiring reimplantation in 5 patients, cystotomy in 1, and bowel injury in 2. Sze HM, Karram MM. Transvaginal repair of vault prolapse: a review. Obstet Gynecol 1997; 89: 466-475. Intraoperative complications with sacrospinous ligament fixation occurred in 9 of 1080 patients, including cystotomy in 4 patients and proctotomy in 5 patients.
[541] ETH-76013 Table 14.3.1.1 Additional Operation Summary
[542] ETH-76016 Table 14.3.1.4 Adverse Events
[543] ETH-75732
[544] ETH-01121
[545] ETH-75906

whether based on the 87 patients who had data at 6 months, or the first 40 patients to get to 6 months (Confidential Statistical Report, TVM Interim Analysis, ETH.MESH.02819245), also exceeded the 20% failure rate – which was a pre-determined cut off to preclude marketing of the Prolift, but was not adhered to (Project D'Art Clinical Strategy, March 20, 2004, ETH.MESH.03354810, Memo to DHF, November 22, 2004, ETH.MESH.00911305). It is entirely plausible that the study results would be even worse if the POPQ system had been used correctly. In addition, as noted above, the number of patients deemed failures differed between the data tables (18 patients) and the 1-year report (16 patients). There were also numerous inconsistencies within the data tables. For example, the number of reoperations was reported as 22 operations in 20 patients (described above) in one table,[546] yet in another table, the number of reoperations was reported as 26 operations in 21 patients.[547]

Even with all these inaccuracies, it was obvious to Ethicon that severe and intractable complications were occurring after the TVM procedure. In just one example, a patient underwent cystoscopy 3 times for symptoms of hematuria, dysuria, recurrent urinary tract infections, and permanent pain. The cystoscopic findings demonstrated deformity of the trigone (the bladder base overlying the TVM mesh implant), and bladder biopsy demonstrated a chronic inflammatory lesion, consistent with the foreign body reaction to the TVM mesh implant.[548] Despite this, Ethicon made no revisions to the Prolift IFU, which did not include "pain" as an adverse reaction, until after FDA review years later.

[546] ETH-76013 Table 14.3.1.1 Additional Operation Summary
[547] ETH-75939, Listing 16.2.7.1, additional operations
[548] ETH-75939-75940

2006, United States TVM study[549] (1-year report: June 28, 2006)

This open-label observational cohort study enrolled 85 patients from 3 sites in the United States[550] and reported 1-year follow-up on 83 patients. Although the US TVM protocol was similar to the protocol for the French TVM study, there were several important differences. Most important, the US TVM protocol allowed study entry of patients with stage II (early) prolapse; 23 of 80 patients (29%) had stage II prolapse preoperatively.[551] The surgical technique was not the same as in the French TVM study, which required that the total mesh implant be used in all patients; the US study protocol allowed surgeons to use only the anterior mesh implant, only the posterior mesh implant, or the total mesh implant. This was reflected in a study amendment in October 2005, well after all subjects had already been enrolled and close to the point when all subjects had already been seen for their 1-year follow-up.[552] However, the surgical protocol in the US TVM study was not consistent with this change and continued to reflect the requirement that the total mesh implant be used.[553] In addition, the US TVM protocol did not require concomitant hysterectomy. This too was not reflected in the surgical protocol that still stated that concomitant or previous hysterectomy was a study requirement.[554]

According to the 1-year report, failure (prolapse ≥ stage II) occurred in 10 of 83 patients (12%).[555] Although the original study protocol defined failure when the upper bound of the 95% confidence interval exceeded 20%,[556] the statistical analysis plans were changed[557] such that the 12-month report changed the definition of failure to the upper bound of the 90% CI exceeding 20%.[558] By changing the original study protocol, Ethicon was able to declare the results of the US study a success, by a margin of four-tenths of a percentage point, with the upper bound of the 90% CI at 19.6% failure. If the original protocol had been followed, the results of the US study would have been deemed a failure, with the upper bound of the 95% CI at 21.0% failure.

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[549] ETH-01155-01228 Clinical Study Report Protocol Number 2003-016 with 1-year follow-up.

[550] In the study protocol, 90 patients were to be enrolled (ETH.MESH.00401351). Data from 5 patients were excluded after Ethicon learned that the patients had been enrolled before IRB approval at that investigational site (ETH.MESH.00401483).

[551] ETH-01194; 5 patients could not be assigned to a prolapse stage because the POPQ measurements for those patients were incomplete.

[552] ETH.MESH.00401344, 10-7-2005; ETH.MESH.00401461, 10-7-2005, email about TVM monitoring visits at last follow-up

[553] ETH.MESH.00401369: heading Use of the Prosthesis: "Use of the continuous prosthesis (monobloc or suture of anterior and posterior TVM) or non-continuous (after section of the mid-portion if the prosthesis is a monobloc one)." Heading Principles of the Procedure: "A prosthesis consisting of both anterior AND posterior portions is used (continuous or non-continuous)."

[554] ETH.MESH.00401369: heading Principles of the Procedure: "A hysterectomy is systematically performed if the patient has not already undergone one."

[555] ETH-01197

[556] ETH.MESH.00401365: "…The upper limit of a 95% confidence interval (CI) for recurrence rate will be used to determine an outcome (success or a failure) for the study. …"

[557] ETH.MESH.00401468

[558] ETH-01184: "… The study would be deemed a success providing the upper 90% two-tailed CI (same as the tail on a one-tail 95% CI) does not exceed 20%. …"

As with the French TVM study, the 12-month report concluded that the intraoperative complication rate (3.5%) was "low."[559] Unfortunately, again as with the French TVM study, the report did not address the extremely high frequency of postoperative adverse events, particularly that of reoperation. A total of 98 adverse events were recorded during the 12-month follow-up, with two-thirds of the patients (56 of 85, 66%) experiencing 1 or more adverse events.[560] A total of 21 of 83 patients (25.3%) required 31 additional operations, including mesh excision in 6 patients (1 patient requiring 3 procedures), repair of rectovaginal fistula, repair of vesicovaginal fistula and ureteral reimplantation, recurrent prolapse repair in 2 patients, and surgery for stress incontinence in 11 patients.[561]

In the 12-month report, vaginal mesh exposure was stated as occurring in 12 patients (14.1%).[562] However, in the data table listing adverse events, 14 patients (16.5%) had vaginal mesh exposure, and 1 patient (1.2%) had visceral mesh erosion.[563] In contrast to the French TVM study, the US TVM study did not describe postoperative vaginal retraction; rather, slightly or moderately reduced vaginal compliance occurred in 3 patients (3.6%). The definition of vaginal compliance and its grading were not described in the study protocol.

Again, as with the French TVM study, the US TVM study had a number of serious limitations, including a disturbingly high frequency of inaccurate measurements of prolapse status using the POPQ system. For example, one table based on data analysis from February 2006 contained 26 entries that were incompatible with the definitions of the POPQ staging system; these inaccuracies were concentrated at David Robinson's investigational site.[564] Considering that the POPQ measurements defined the primary study endpoint of success or failure, this markedly high frequency of errors introduces doubt as to whether the study results can be trusted. In addition, the US TVM study was deemed a "success" by a margin of only four-tenths of a percentage point after the threshold was changed from a 95% to 90% confidence interval; it is likely that the study would have been a failure, as with the French TVM study, if the POPQ system had been used correctly and if Ethicon had not violated the original study protocol that defined the primary endpoint by a 95% confidence interval.

As discussed above, the POPQ system for staging prolapse has several important limitations, including a strong subjective component. In the case of the TVM studies, it is plausible that surgeons with substantial personal and financial bias in showing the success of the TVM procedure were prone to accepting less than maximal effort during POPQ measurements after the TVM procedure, thereby underestimating the true extent of postoperative prolapse. Whether due to a conscious bias or otherwise, the literature has clearly demonstrated that

[559] ETH-01206
[560] ETH-75709, Table 14.3.1.4 Adverse Events
[561] ETH-75076, ETH-75776
[562] ETH-01204
[563] ETH-75710 Table 14.3.1.5 Adverse Events by Code
[564] ETH-75580; of the 26 inaccurate POPQ entries, 24 of 26 occurred at the site JM10 (Robinson, 30 enrolled patients) and 1 each at site JM20 (Miller, 28 enrolled patients) and 3006 (Lucente, 27 enrolled patients)

financial conflicts of interest influence the reporting of results.[565] The lack of independent observers represents another critical flaw in the study methodology that Ethicon developed to study the TVM procedure.[566] Even the wording of the objective of the TVM studies revealed Ethicon's bias that the study's results would support the foregone conclusion that the TVM procedure would be confirmed as effective.[567] In sound clinical research design, the purpose of a study is to evaluate outcomes, not to "demonstrate" them.

Considering the French and US TVM studies as a whole, critical aspects of study design and management were so flawed that it again raises serious questions as to whether the study results can be trusted at all. There was continuing confusion over what constituted the definition of the primary endpoint, such that the protocol had to be amended to clarify it, with the addition of reoperation for recurrent prolapse added to the original definition of failure as ≥ stage II prolapse.[568] This study amendment was added in October 2005, well after all subjects had already been enrolled and close to the point when all subjects had already been seen for their 1-year follow-up. Although this amendment was made for clarification, this introduced a new level of confusion into data collection, regarding how to handle patients with failure at one time-point, followed by "success" at a later time-point. Ethicon finally clarified that a "success" by POPQ would be deemed a failure if the patient underwent reoperation for recurrent prolapse in the intervening time period.[569] However, Ethicon never addressed the situation where patients failed by POPQ at 6-month follow-up yet "succeeded" by POPQ at 1-year follow-up without an intervening reoperation for recurrent prolapse. This situation occurred among several patients,[570] and at least in the US TVM study, these 2 patients were not counted as failures.[571] If these 2 patients had been categorized correctly as failures, the US TVM study as a whole would have been deemed a failure.[572]

In addition, there was confusion at the investigational sites as to whether reoperation for recurrent prolapse constituted a failure if the reoperated vaginal compartment had not had mesh placement at the index surgery, although the study protocol clearly indicated that was a

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[565] Als-Nielsen B et al. Association of funding and conclusions in randomized drug trials: a reflection of treatment effect or adverse events? JAMA 2003; 290: 921-928.
Jorgensen AW et al. Cochrane reviews compared with industry supported meta-analyses and other meta-analyses of the same drugs: systematic review. BMJ 2006; 333: 782. Epub Oct 6 2006.
Jorgensen AW et al. Industry-supported meta-analyses compared with meta-analyses with non-profit or no support: differences in methodological quality and conclusions. BMC Med Res Methodol 2008; 8: 60-67.
[566] Antosh DD et al. Outcome assessment with blinded versus unblended POP-Q exams. Am J Obstet Gynecol 2011; 205: 489.e1-4. Epub July 20, 2011. Overall prolapse recurrence was 15% higher when assessed by an independent observer than by the operating surgeon.
[567] ETH.MESH.00401354, TVM protocol, Objective: "The study will **demonstrate** the usability of Gynecare Gynemesh Prolene Soft (polypropylene) mesh for anterior, posterior and vault prolapse repair, using the TVM technique." (emphasis added)
[568] ETH.MESH.00401344
[569] ETH.MESH.00401498
[570] ETH-75916-75917; ETH-75591-75592
[571] ETH-01197
[572] ETH.MESH.00401365

failure.[573] Some Ethicon documents implied that the investigators could determine success or failure, independent of the actual POPQ measurements.[574] In further confirmation of the inaccuracy of POPQ measurements in the TVM studies, Ethicon staff were creating data checks for POPQ points as late as September 2005, again well after all subjects had already been enrolled and close to the point when all subjects had already been seen for their 1-year follow-up.[575] Ethicon staff struggled to reconcile POPQ data mismatches while trying to perform data analysis, yet the data tables still contained numerous inaccuracies, as described above.[576] Data forms for unscheduled visits, most likely related to patients' symptoms and complications, were only being developed in September 2005.[577] Furthermore, adverse events were not recorded consistently and accurately.[578]

Ethicon never established a data safety and monitoring committee to oversee the TVM studies, which is another egregious breach of ethical standards in the performance of clinical research. The informed consent documents used in the TVM studies had numerous deficiencies and inaccuracies. Three of the 4 informed consent forms do not clearly identify Ethicon as the sponsor of the study.[579] The experimental aspect of the research was not stated in the consent form for the French TVM study, and in the 3 consent forms for the US TVM sites, it was misstated as merely a modification of similar procedures used to treat prolapse.[580] This was directly contradicted by Ethicon's marketing claims of the Prolift procedure as a "new" and "revolutionary" procedure.[581] The TVM procedure, as the forerunner to the Prolift procedure, was emphatically NOT similar to other procedures performed to treat prolapse. Ethicon's description of the experimental aspect of the TVM studies misled women into expecting a

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[573] ETH.MESH.00401511

[574] ETH.MESH.00401455: Email string 1-30-2006 regarding confusion about reporting failures of recurrent prolapse even if asymptomatic, from Natalie Tayse to Judith Gauld: "… if the PI felt it was not a failure, they could answer on the query that it is asymptomatic, and they would not have to complete an AE form. I am getting a little confused."
ETH.MESH.00401530: Email 8-22-2005 about failure of patient 04007 in French TVM study, from Rodolphe Blin: "I know that -1 [cm] for the Ba score [failure] is the limit between grade 1 and 2 but Dr. Cosson confirm to me the grade 1 [success]."

[575] ETH.MESH.00401476, ETH.MESH.00401490

[576] ETH.MESH.00401449

[577] ETH.MESH.00401489, ETH.MESH.00401481

[578] ETH.MESH.00401469, ETH.MESH.00401479, ETH.MESH.00401485, ETH.MESH.00401491

[579] ETH.MESH.00401781, Robinson; ETH.MESH.00402062, Miller; ETH.MESH.02812974, French TVM study

[580] ETH.MESH.00401781, Robinson, Participation: "The experimental aspect of this study is the actual procedure your doctor will be using, which is a modification of similar procedures that have been used to treat problems of this type."
ETH.MESH.00402285, Lucente, Purpose of the Study: "The purpose of the study is to evaluate a different way to surgically place the mesh. The procedure is similar to the one already used but it has been slightly changed in hopes that the mesh will work better for a long period."
ETH.MESH.00402062, Miller, Purpose: "The experimental aspect of this study is the shape of the mesh and the technique for attaching the mesh. The exact shape of the mesh used is a modification of similar procedures that have been used to treat problems of this type."
ETH.MESH.02812974, French TVM study: no indication of the experimental nature of the research.

[581] ETH.MESH.00011654

procedure that was similar or only slightly changed relative to traditional vaginal prolapse surgery.

The risk section of the informed consent documents was also worded in a way that would mislead women. In one document, risks were not attributed to the TVM procedure at all.[582] In another, after listing risks "associated with every other standard mesh," the document stated that there were no other risks of the study.[583] In addition, the risk of mesh exposure was either not stated[584] or was intentionally understated, described as "rare"[585] or "less frequent."[586] As discussed elsewhere in this report with regard to the use of the term "rare" in Ethicon's patient brochures promoting Prolift,[587] using the term "rare" is ambiguous to the extent it does not provide a quantitative estimate of the risk of mesh exposure. Nevertheless, to suggest that anyone would equate the term "rare" with a known mesh exposure frequency of at least 10% is disingenuous at best. In addition, the informed consent documents did not provide specific information as to the frequent need for surgical treatment, the possible need for 2 or more operations, and the associated symptoms of vaginal mesh exposure, including pelvic pain, dyspareunia, and vaginal bleeding or discharge. The informed consent documents did not provide information about any other mesh-related complications, particularly mesh retraction, and provided no information about surgical risk related to the use of inserter tools for Gynemesh PS mesh implantation.

Of interest, the US informed consent documents did warn of "problems with urination, either incontinence or difficulty with urination."[588] However, this was attributed to "change in the position of your bladder," as opposed to nerve damage related specifically to the TVM procedure itself. Clearly, Ethicon understood the risk of "problems with urination" as a result of the TVM procedure and consequently the Prolift procedure, yet Ethicon failed to warn physicians and patients of this risk in the original Prolift IFU and Prolift marketing materials directed to physicians and patients.

These unsound and unethical breaches in study design and management, as well as inexcusable deficiencies in data collection and monitoring, emphasize the poor quality of data

[582] ETH.MESH.00402285, Lucente, Discomforts and Risks: "Your doctor will carefully describe the risks associated with this type of surgery. These risks are not because of the study."
[583] ETH.MESH.02812074, French TVM study: "There are no supplementary risks associated with your participation in this study."
[584] ETH.MESH.02812974, French TVM study
[585] ETH.MESH.00401781, Robinson, Risks: "A reaction to the mesh material, including material exposure that may require removing some or all of the mesh may rarely occur."
ETH.MESH.00402062, Miller, 6th bullet: "Rarely, a reaction to the mesh material may occur, including material exposure that may require removing some or all of the mesh."
[586] ETH.MESH.00402285, Lucente, Discomforts and Risks: "The following are less frequent … Some subjects may have discomfort from the mesh or erosion (wearing through of the mesh) …"
[587] ETH.MESH.00016666
[588] ETH.MESH.00401781, Robinson; ETH.MESH.00402062, Miller; ETH.MESH.00402285, Lucente, worded as "problems with urination and control of urination" without attribution. The informed consent document for the French TVM study does not mention any risks related to urination.

produced by the Ethicon TVM studies, hardly the type of data to be used to support the introduction of the Prolift procedure, a new product and procedure with markedly different and increased risks compared with traditional vaginal prolapse surgery.

In fact, full data from the TVM studies were NOT available to support the launch of the Prolift product and procedure. Given that marketing of Prolift began in March 2005, the only results from the TVM studies at that time were very limited, consisting of 6-month follow-up in 40 patients from the French TVM study (failing the primary endpoint) and 29 patients from the US TVM study.[589] Considering that the Prolift procedure was untested and the permanent Prolift mesh implant carried a life-long risk of complications, Ethicon showed an appalling disregard for the well-being of women in marketing the Prolift procedure with so few data. As became obvious with longer-term evidence (discussed below), the frequency of complications increased markedly year after year, particularly for those complications that required reoperation.

2006, Fatton et al[590,591]

This abstract and article represent a retrospective chart review of 110 women who had undergone the Prolift procedure between February and September 2005. The article described the surgical technique used, which was similar but not identical to the technique described in the Prolift surgical technique document. For example, in the article, placement of the posterior cannula-equipped guide was described as passing through the "middle part of the sacrospinous ligament," as opposed to "3-4 cm medial to the ischial spine" as stated in the Prolift surgical technique document.[592] In addition, 5 patients underwent traditional sacrospinous ligament fixation in conjunction with the anterior Prolift procedure for large cystocele and excessive uterine mobility without rectocele. This serves to emphasize the inadequacy of the anterior Prolift procedure alone to provide adequate apical support and the reluctance of surgeons to perform a posterior Prolift procedure for apical support in the absence of posterior vaginal prolapse.

The authors used a unique system to describe the extent of prolapse, the Jacquetin system, which was described as a modification of the Baden and Walker half-way system. The Jacquetin classification has 6 stages, with stages I, II, and III corresponding approximately to POPQ stages I and II; and stages IV, V, and VI corresponding to POPQ stages III and IV. Preoperatively, all patients had Jacquetin stage III or IV prolapse, which by the POPQ standard would be stage II or early stage III (prolapse limited to 3 cm beyond the hymen). In addition, only 20% of the study population had previously undergone surgery for prolapse; therefore, the

[589] ETH.MESH.00401468
[590] ETH-02653: Fatton B et al. Preliminary results of the "Prolift" technique in the treatment of pelvic organ prolapse by vaginal approach: A multicentric retrospective series of 110 patients [abstract]. Int Urogynecol J 2006; 17 (Suppl 2): S212-213.
[591] ETH-02358: Fatton B, Amblard J, Debodinance P, Cosson M, Jacquetin B. Transvaginal repair of genital prolapse: preliminary results of a new tension-free vaginal mesh (Prolift™ technique) - a case series multicentric study. Int Urogynecol J 2007; 18: 743-752. Epub 11-28-2006.
[592] ETH.MESH.00419581

majority of the study population was undergoing the Prolift procedure for primary prolapse repair of a relatively early stage. In addition, the range of age extended as low as 29 years in this study population.

Duration of follow-up for 106 patients was short, a median of 25 weeks (range, 12-42 weeks). Nevertheless, at least 8 patients (7.5%) required reoperation in that short time, including surgical drainage of postoperative hematomas in 2 patients, mesh excision due to exposure in 2 patients, and reoperation for recurrent prolapse in 4 patients. In one patient who required surgery for recurrent prolapse and urinary retention, anterior vaginal prolapse had recurred anterior to the interureteric ridge after caudal retraction of the anterior mesh. Other complications were reported in 18% of patients without stating the type of treatment, including 18 patients with mesh shrinkage and 1 patient with vaginal synechia (scarring). Postoperative catheterization for impaired bladder emptying was required in 6 patients for up to 73 days after the Prolift procedure. Among 30 patients known to be sexually active before the Prolift procedure, almost one-quarter had not resumed sexual intercourse by 3 months, and 3 of 23 patients (13%) complained of dyspareunia.

Although the authors stated in the Discussion section of the article that "… at the present time and with a 5-years experience with TVM, no patients developed such adverse events [mesh erosion into bladder or rectum]," this was not true. Such serious adverse events had occurred in the French and US TVM studies, including 2 patients who required 3 operations for repair of vesicovaginal fistulas and ureteral reimplantation, and 1 patient who required 2 operations for repair of rectovaginal fistula.[593] It is particularly disturbing that these authors would offer such false reassurance, considering the seriousness of these complications due to the Prolift procedure.

Failure (recurrent prolapse) was defined as asymptomatic stage 3 or 4 prolapse (by the Jacquetin system) or any symptomatic prolapse; failure occurred in 5 patients (4.7%) by 3 months of follow-up. The authors recommended that "Anatomical and functional results must be assessed with a long-term follow-up to confirm the effectiveness and safety of the procedure." Considering that this article was published almost 1 year AFTER launch of the Prolift procedure and considering the high frequency of complications, especially reoperation, with such short follow-up, these results support the necessity of long-term study of the Prolift procedure BEFORE it was widely introduced to the clinical community.

In addition, the authors concluded that "We have to assess more precisely functional and sexual outcomes before to extend the indications of Prolift to young women or for primary prolapse repair." This apparently reflects concern on the part of the authors regarding complications seen in these 2 subsets of patients, young women and women undergoing primary prolapse repair, that suggests the risks outweighed the benefits for those women. Of interest, these were some of the conclusions reached by professional organizations years later, after the second FDA public health notification about risks of transvaginal mesh, when it became even more evident that the risks did not outweigh the benefits for the majority of

[593] ETH-76013, ETH-75776

patients with prolapse and that transvaginal mesh implantation should be restricted to only certain groups of women.[594] Axel Arnaud testified regarding this language and confirmed that the Prolift was not the best option for sexually active women, and this was also stated in an internal powerpoint that states for a sexually active woman the procedure of choice should be suture repair. (Axel Arnaud Dep. Tr., 467:25-468:7, 480:22-481:17). Similarly, Paul Parisi, the professional education corporate representative, testified regarding an internal powerpoint indicating that a young patient, aged 30-55, who wants to maintain sexual function, should have a suture procedure or sacrocolpopexy. (Paul Parisi Dep. Tr. 246:21-249:15; ETH.MESH.03642757) Nevertheless, Ethicon never addressed patient selection criteria to communicate this information in its 2005 Prolift professional education, or anywhere else at any time, and continued to market to physicians and patients that the Prolift procedure was "appropriate for almost all patients."[595] Improper patient selection is a factor that will result in an even worse risk benefit profile since, as recognized by Piet Hinoul in his report in 2012 regarding the mesh device, if a patient is not properly selected the risk benefit profile is unacceptable.

The abstract stated that industry did not support this work; the article did not report any financial support for the study or any financial conflicts of interest for the authors.

2006, Cosson, et al.

This article, Les prostheses synthetiques dans la cure de prolapses genitaux par la voie vaginale: bilan en 2005; J Bynecol Obstet Biol Reprod 2006; 35 (cahier 1): 429-454, is written in French but contains an abstract/summary in English. The article details a literature review by Cosson and other members of the TVM group. Most relevant, the authors concluded that the effort to reduce the frequency and severity of contraction, erosion, and dyspareunia with the use of Prolene Soft, "does not appear to fulfill expectations." They go on: "the lack of data on the rate of complications and patient quality of life is unacceptable for this functional surgery. We still have reservations about widespread use of synthetic meshes." These strong statements were published more than one year after the Prolift was already on the market for widespread use. The authors conclusions are correct – the use of Prolene Soft mesh through the TVM technique/Prolift was medically unsafe, with an unacceptable risk benefit profile.

[594] Vaginal placement of synthetic mesh for pelvic organ prolapse. Committee Opinion No. 513. American College of Obstetricians and Gynecologists. Obstet Gynecol 2011; 118: 1459-1464.

[595] ETH.MESH.00769060, Gynecare.com copy, ETHIN-0004-0013, created August 17, 2006: "Am I a candidate for Gynecare Prolift? Pelvic floor repair procedures with Gynecare Prolift are appropriate for almost all patients…"
ETH-00264, Marketing materials for Prolift directed to patients, copyright 2006: "It [the Prolift procedure] is appropriate for almost all patients …"
ETH-00761-00787, Ethicon cooperative advertising, providing marketing materials directed to patients that can be personalized with a doctor's name, address, and logo: "And it [the Prolift procedure] is appropriate for almost all patients …"

2008, Cosson et al[596]

This abstract represented a retrospective study of 217 patients with mean follow-up of 10 weeks after Prolift procedures and compared findings among women who had previous hysterectomy (n=53) versus women who chose uterine conservation (n=164). The abstract goes on to describe 23 women who had concomitant hysterectomy, although it is not clear whether this represents an error in the total study population or some other error.[597] The abstract reported recurrent prolapse (defined as ≥ POPQ stage II) significantly more frequently in women after the Prolift procedure with uterine conservation (13 of 164, 8%) compared with none in 53 women who had previous hysterectomy. Recurrent prolapse was even more frequent in women with concomitant hysterectomy (4 of 23, 17.4%), but this difference did not reach statistical significance due to low numbers. The frequency of vaginal mesh exposure did not differ, but mesh contraction occurred more frequently in women with uterine conservation (32 of 164, 20%) and previous hysterectomy (11 of 53, 21%), versus women having concomitant hysterectomy (2 of 23, 9%). The authors concluded that "keeping the uterus seems interesting but needs to be strictly evaluated by prospective comparative studies."

2010, Jacquetin et al[598]

This study presented 3-year follow-up on 85 of the 90 women (94%) enrolled in the French TVM study. Although the abstract stated that women with ≥ stage II prolapse were enrolled, the text of the Methods section stated that women had prolapse at least 1 cm beyond the hymen (stage III). Of the 90 women enrolled, 14 women (16.3%) had stage II prolapse. The authors reported failure (recurrent prolapse > stage I) in 15 of 86 women (17.4%) at 1-year follow-up, including 1 woman with reoperation for recurrent prolapse. However, this was not consistent with data from the 1-year analysis of the French TVM study, in which 18 of 87 women (20.7%) had recurrent prolapse, including 2 women with reoperation for recurrent prolapse.[599] The authors then reported failure in 17 of 85 women (20%) at 3-year follow-up, including 3 women with reoperation for recurrent prolapse. Since it is impossible for the number of women categorized as failure to decrease with time, this represents accidental or intentional misreporting of the results of the French TVM study.

In addition, there were substantial inconsistencies in the reporting of complications. The authors reported in this article that 12 of 90 patients (13.3%) required reoperation, 3 for recurrent

[596] Cosson M et al. Preservation of uterus when treating prolapse by Prolift TM does not significantly reduce risk of early post surgical complications and failures [abstract]. Int Urogynecol J 2008; 19 (Suppl 1): S92. Presented at the September 2008 meeting of the International Urogynecologic Association.
[597] Study population = 217 patients yet 53 + 164 + 23 = 240 patients.
[598] ETH.MESH.01205254: Jacquetin B et al. Total transvaginal mesh (TVM) technique for treatment of pelvic organ prolapse: a 3-year prospective follow-up study. Int Urogynecol J 2010; 21:1455-1462. Epub Aug 4 2010.
[599] ETH-75906

prolapse, 8 for mesh exposure, and 1 with vesicovaginal fistula.[600] However, within the text of the article, 4 other patients (for a total of 16 of 90, 17.8%) were described who required reoperation, including 1 patient each with urinary retention requiring mesh release, evacuation of hematoma, hematoma leading to mesh extrusion requiring mesh resection, and mesh retraction requiring resection. Furthermore, these data did not include 14 additional patients (for a total of 30 of 90, 33.3%) who required reoperation within the first year of follow-up, including 9 patients treated with TVT-O for new stress incontinence, 1 patient with section of TVT-O for voiding impairment, 1 patient with section of vaginal adhesions, and 3 patients requiring other operations.[601] Therefore, the authors underreported the frequency of reoperation by a factor of 2.5 times.[602]

In the Discussion section of the article, the authors stated that "A meta-analysis by Diwadkar et al. calculated a lower re-operation rate for prolapse (1.3%), but a higher total reoperation rate (8.5%) after mesh kits. This can possibly be attributed to a shorter follow-up time (26 months) and the fact that Diwadkar's study reflects outcomes after fully standardised mesh kits. These series will be less impacted by learning curves reflected in this series and the fact that the addendum of cannula's [sic] may affect the erosion rates as we discuss later." The authors seem to completely misunderstand the true implication of the shorter follow-up after mesh kits; the relatively low reoperation rate for prolapse may be attributed to the short duration of follow-up, but this would be expected to increase with time. Indeed, in this article, the authors reported an almost doubling of recurrent prolapse between 6 months (11.6%) and 3 years (20%), which doesn't even account for the inconsistencies between the data in this article and Ethicon's report of 1-year data, as described above. In addition, because permanent mesh implantation introduces a life-long risk of mesh-related complications, the total reoperation rate after mesh kits can only be expected to rise with time. Furthermore, the authors propose that the results in this series were affected by "learning curves"; if the very inventors of the TVM procedure can claim an effect on results due to a learning curve, this only emphasizes the certainty that outcomes will be even more markedly affected when the Prolift procedure, based on the TVM procedure, became widely used by members of the surgical community with varying levels of skill and, by definition, with inexperience in performing the Prolift procedure.

The authors conclude that "Medium-term results demonstrate that the TVM technique provides a durable prolapse repair." However, they provide no summary statement to indicate the human cost of achieving this "durable prolapse repair," including reoperation in fully one-third of the patients and loss of sexual activity in 41%. In addition, these women carry a life-long risk of developing mesh-related complications, as well as developing recurrent prolapse. It is likely that the authors avoided drawing any conclusions regarding the risk-benefit ratio of the TVM procedure, because any (unbiased) observer would have to conclude that the risks far outweigh

[600] ETH-75939: The patient with vesicovaginal fistula required 2 operations, one for repair of vesicovaginal fistula and the other for ureteral reimplantation.
[601] ETH-76013, ETH-75939-75940: The 3 other operations comprised examination under anesthesia, cholecystectomy, and cystoscopy performed 3 times in 1 patient.
[602] 33.3% divided by 13.3% = 2.5 times

the benefits. Furthermore, since the risks are ongoing and life-long, and the benefit will continue to erode with time, the risk-benefit ratio can only worsen over time.

2010, Velemir et al[603]

This study by the French TVM group assessed 91 women at least 1 year after the Prolift procedure, which included 75 anterior and 62 posterior Prolift mesh implants. Mesh retraction was estimated by palpation relative to the original length of the mesh and was defined qualitatively as absent, moderate (< 50%), or severe (≥ 50%). In addition, ultrasonography was performed to measure mesh length and thickness. Anterior mesh retraction was moderate in 80% and severe in 9.3% of patients. Posterior mesh retraction was moderate in 48.4% and severe in 9.7% of patients. With both anterior and posterior Prolift mesh implants, mesh retraction was strongly associated with increased mesh thickness and higher frequency of recurrent prolapse. In the 7 patients with severe anterior mesh retraction, maximum mesh thickness was 4.1 ± 0.9 mm, and 5 of the 7 patients (71%) had recurrent anterior vaginal prolapse. In the 6 patients with severe posterior mesh retraction, maximum mesh thickness was 4.6 ± 1.3 mm, and 3 of the 6 patients (50%) had recurrent posterior vaginal prolapse. The relations in the groups with moderate mesh retraction were similar albeit to a lesser degree. In patients without anterior mesh retraction, which was only 8 patients, maximum mesh thickness was 2.0 ± 0.3 mm, and none had recurrent anterior vaginal prolapse. Similar findings were reported for the 26 patients without posterior mesh retraction.

The authors described and depicted that severe mesh retraction resulted in lack of mesh covering the distal (closer to the vaginal opening) bladder and rectum, leading to recurrent prolapse. The authors felt this explained why the frequency of recurrent prolapse increased between 3 months and at least 1 year after the Prolift procedure, due to ongoing mesh retraction caused by the chronic inflammatory and foreign body reaction. The authors also stated that mesh retraction was probably a factor contributing to postoperative pain and dyspareunia, although clinical correlation with pain was not reported in this study. The authors did not discuss why moderate mesh retraction was nearly twice as frequent with the anterior versus the posterior Prolift mesh implant. The clinical outcomes for these patients were presented in 2009, including a 19.6% painful vaginal examination rate, which is very high and demonstrates an unacceptable level of risk. (Velemir, et al.; Mesh Shrinkage: How to assess, how to prevent, how to manage?, IUGA, Como, Italy, June 16-20, 2009; Deposition exhibit P1271, Trial exhibit P1706).

Based on these findings, the authors modified the Prolift technique to include suturing the anterior mesh to the pubococcygeus muscles and placing the posterior mesh to cover the anorectal junction. The authors acknowledged that they don't yet know if these modifications will prevent mesh retraction. In addition, the authors cited a study in which prolapse recurred

[603] Velemir L et al. Transvaginal mesh repair of anterior and posterior vaginal wall prolapse: a clinical and ultrasonographic study. Ultrasound Obstet Gynecol 2010; 35: 474-480.

despite the fact that the anterior mesh had been sutured to the bladder base.[604] Ultrasound findings in that study suggested dislodgement of the superior anchoring mesh arms. (See below for a detailed review of the Shek et al study.)

The results of this study and others show clearly that the Prolift procedure is not a finished product, and surgeons continue to invent modifications in an attempt to avoid inevitable mesh-related complications. That this is occurring under the label of clinical practice is an egregious breach of ethical standards in distinguishing between clinical care and clinical research. Patients undergoing the Prolift procedure are being experimented on without their knowledge and without their explicit consent and agreement to participate in this experimentation. Ethicon marketed the Prolift procedure as "new" and "revolutionary" without the least understanding of how the Prolift mesh implant would behave in the vaginal environment. Ethicon knew that mesh retraction caused serious clinical consequences in hernia repair, and Ethicon had to know that those serious clinical consequences would occur at the same level, if not worse, in vaginal prolapse repair. From the first reports of the TVM technique using Gynemesh PS mesh, mesh retraction was known to be a frequent and serious complication, yet beyond a mere generic statement in the Prolift IFU,[605] Ethicon failed to warn surgeons and patients of the severe clinical consequences and lack of effective prevention or treatment of mesh retraction.

2011, Miller et al[606]

This study reported the 5-year results for 66 of 85 patients (78%) originally enrolled in the US TVM study. A total of 15 of 66 patients (22.7%) met criteria for failure in the treated compartment, including 10 patients with ≥ stage II prolapse and 5 patients requiring reoperation for recurrent prolapse. However, the authors of this study presented a secondary outcome as if it were primary; the primary endpoint in the original study protocol included failure at any vaginal site and did not distinguish between overall failure versus failure only in the mesh-treated compartment.[607] Overall failure occurred in 33.3% (90% CI, 23.8-44.1%). Although the authors claimed that these results demonstrate stability of the anatomic outcomes, in fact, the TVM failure rate nearly tripled from 1 year (12%) to 5 years (33.3%).

This article contained numerous inconsistencies compared with earlier TVM data. Most importantly, the authors did not include 10 patients who required surgery within the first year of follow-up,[608] thereby minimizing the true frequency of reoperation necessary after the TVM procedure. In addition, the authors reported data inaccurately to underrepresent the true

[604] PLTMEDLIT01247 (cited in ETH-02314): Shek KL, Dietz HP, Rane A, Balakrishnan S. Transobturator mesh for cystocele repair: a short- to medium-term follow-up using 3D/4D ultrasound. Ultrasound Obstet Gynecol 2008; 32: 82-86. Epub 10 June 2008.
[605] ETH.MESH.02341527, Prolift IFU, Adverse Reactions: "… scarring that results in implant contraction."
[606] Miller D et al. Prospective clinical assessment of the transvaginal mesh technique for treatment of pelvic organ prolapse – 5 year results. Female Pelvic Med Reconstr Surg 2011; 17: 139-143.
[607] ETH.MESH.004011351
[608] ETH-75776

frequency of complications by using the total study population of 85 women as the denominator in reporting the frequency of complications, rather than the appropriate denominator of 66 women who attended 5-year follow-up. For example, mesh exposure was reported as 19% (16 of 85 patients), rather than the true frequency at 5 years of 24% (16 of 66 patients). Belying Ethicon's claim that mesh exposure is transient and related to defective wound healing,[609] 4 women had persistent mesh exposure at 5 years. In addition, voiding dysfunction was misreported as 9% (8 of 85 patients), rather than the true frequency at 5 years of 12% (8 of 66 patients). One woman had persistent voiding dysfunction at 5 years. The original Prolift IFU had no warning regarding voiding dysfunction, and the Prolift IFU revised after FDA review only stated that normal voiding could be impaired "for a variable length of time,"[610] and did not indicate that voiding dysfunction could be prolonged, if not permanent.

Although the authors claimed that the most important finding of their study was "… the lack of new morbidity after the early (1 year) postoperative period," it would be more accurate to state that the same type of morbidity occurred again and again over the 5-year period. As reported in this article, a total of 29 of 66 women (44%) required reoperation, including 13 for stress incontinence, at least 9 for mesh exposure, 5 for recurrent prolapse, and 2 for fistulas, although the authors did not state this finding directly. Furthermore, this number did not include 10 additional patients who required surgery within the first year of the TVM procedure. Since the number of women requiring more than one operation for complications was not stated, it is not possible to determine whether 39 of 66 women (59%) required reoperation or whether some fewer number of women required 39 operations. Either way, this frequency of reoperation for complications is exceedingly high and vastly higher than anything reported with traditional vaginal prolapse surgery or even abdominal prolapse surgery.[611]

In addition, the authors did not report mesh retraction. Given that moderate or severe mesh retraction was reported in two-thirds of anterior and posterior Prolift mesh implants,[612] it is utterly implausible that mesh retraction did not occur in this patient population as well. This serious deficiency in reporting leads to an underestimate of the already considerable mesh-related morbidity.

Consistent with the 3-year results of the French TVM study, nearly one-third of preoperatively sexually active women abandoned sexual activity after the Prolift procedure, which strongly suggests that the TVM procedure impaired sexual activity in ways that were not assessed. However, the authors did not present the data in such a way that it was obvious that nearly one-third of the women (13 of 40, 32.5%) stopped being sexually active, and they did not

[609] ETH-60160, email from Scott Jones, 12-7-2005: " … exposure refers to defective wound healing, which may not have anything to do with the graft, but rather with the quality of a patients [sic] tissue. Remember, exposures are temporary and can be conservatively managed."
[610] ETH.MESH.02341735
[611] PLTMEDLIT00139: Diwadkar GB, Barber MD, Feiner B, Maher C, Jelovsek JE. Complication and reoperation rates after apical vaginal prolapse surgical repair: a systematic review. Obstet Gynecol 2009 Feb; 113: 367-373.
[612] Velemir L et al. Transvaginal mesh repair of anterior and posterior vaginal wall prolapse: a clinical and ultrasonographic study. Ultrasound Obstet Gynecol 2010; 35: 474-480.

discuss this in the article. Instead, by stating that only 1 woman developed new dyspareunia after the TVM procedure, the authors had the audacity to claim that their results "seem to confirm a net positive effect on sexual activity following prolapse surgery despite the use of mesh."

The authors stated that since "the 3-year time point was predictive of the 5-year results," that would be a more practical end-point for future studies because of significant loss to follow-up. First, significant loss to follow-up is not inevitable; in the French TVM study, 94% of patients returned for 3-year follow-up. More importantly, however, this view disregards the life-long risk of mesh-related complications and need for treatment, most often operative treatment. Studies have clearly demonstrated that patients with complications often change doctors without explanation, leaving the original operating surgeon with an unrealistic and positively skewed view of the outcomes of his or her surgery (see Blandon et al, discussed below). In addition, limiting follow-up to 3 years would fail to capture new recurrent prolapse and its need for treatment, as seen in this study between 3 and 5 years.

The authors concluded that "Five-year results indicated that TVM provided a stable anatomic repair." As discussed above, this is not true. However, as with the conclusions drawn from the 3-year results of the French TVM study, they provide no summary statement to indicate the human cost of achieving this so-called "stable anatomic prolapse repair," including reoperation in nearly half of the patients and loss of sexual activity in one-third of the patients. Indeed, the reoperation rate after the TVM procedure increased markedly over time, from 23-25.3% at 1 year, 33.3% at 3 years,[613] and at least 44% at 5 years. Given the life-long risk of mesh-related complications and the deterioration of "benefit" as prolapse recurs over time, it is obvious that the risks of the TVM procedure greatly outweigh the benefits. That Ethicon didn't study the TVM technique for an acceptable period of time before rushing to market with the Prolift procedure is a clear indication of putting business concerns ahead of patient safety.

In summary, the authors misrepresented their data to present the results of the TVM procedure in the best possible light, by focusing on results that did not represent the primary endpoint in the study protocol; by misreporting the number of women requiring reoperation; by calculating percentages with the wrong denominator to underestimate the true frequency of complications; by ignoring mesh retraction to underestimate mesh-related morbidity; and by ignoring the high proportion of women who abandoned sexual activity yet claiming "a net positive effect on sexual activity." Given the nature and frequency of these misrepresentations, along with the strong financial bias among the authors (including at least one Ethicon employee and other Ethicon-paid consultants), serious questions about the credibility of these results must be raised. The article did not include any author disclosures of financial conflict of interest, and it did not identify the study sponsor as Ethicon.

[613] Jacquetin B et al. Total transvaginal mesh (TVM) technique for treatment of pelvic organ prolapse: a 3-year prospective follow-up study. Int Urogynecol J 2010; 21:1455-1462.

2012, De Landsheere L et al[614]

This study reported the results of a retrospective study after the index procedure was performed between January 2005 and January 2009, with follow-up of a median of 38 months (range, 15-63 months) in 524 women after Prolift procedures, including 48 women (9%) after anterior Prolift, 103 women (20%) after posterior Prolift, and 373 women (71%) after total Prolift procedures. In 286 women, anterior and posterior Prolift procedures were performed with uterine conservation. Of a total of 600 women in the consecutive series, 68 women were lost to follow-up, and 8 women died (including 1 woman who died of endometrial cancer 3 years after Prolift with uterine conservation). Of the 76 women not included in the primary analyses, 7 women (9.2%) had post-Prolift surgery. In the study population, 98 of 524 women (18.7%) had previous surgery for prolapse; therefore, the majority of women were having primary repair of prolapse. The overall preoperative stage of prolapse was not reported. Intraoperative complications included bladder injury in 3 patients and rectal injury in 1 patient (overall visceral injury, 0.8%).

Overall, 76 of 524 patients (14.5%) required reoperation after the Prolift procedure, although the article reported that only 61 of 524 patients (11.6%) required reoperation. The authors opted not to include 5 patients in the total, including 3 patients who required immediate postoperative surgery for ongoing blood loss and 2 patients who were treated with hysterectomy for postmenopausal bleeding (with benign findings). However, the difference between 61 patients as reported and 71 patients with reoperation, besides the 5 patients just mentioned, is apparently a simple error.

The most common indication for reoperation was for continence issues. A total of 36 women underwent 37 operations related to urinary issues, including 23 women treated with sling surgery for stress incontinence (within 16 months of the index Prolift procedure), 2 women with recurrent stress incontinence, 7 women with persistent stress incontinence, 1 woman requiring sling adjustment, and 3 women with sling mesh exposure who underwent partial sling excision; of these 3 women, 1 woman was subsequently treated with another sling for recurrent stress incontinence.

A total of 19 women had reoperation for mesh complications, including 13 women with mesh exposure (within a median of 13 months from the index Prolift procedure), 1 woman with infected mesh (who subsequently developed recurrent prolapse after complete mesh excision), 2 women with mesh retraction, 2 women with rectal compression, and 2 women with vaginal synechia. One of these women had both mesh retraction and mesh exposure. In addition, 16 women had reoperation for recurrent prolapse within a median of 23 months from the index Prolift procedure.

[614] De Landsheere L et al. Surgical intervention after transvaginal Prolift mesh repair: retrospective single-center study including 524 patients with 3 years' median follow-up. Am J Obstet Gynecol 2012; 206: 83.e1-7.

Although this article reports a lower frequency of reoperation than other articles, it must be emphasized that this represents the work of the TVM group that has the longest experience in performing transvaginal mesh prolapse surgery, by first inventing the TVM procedure and then using the Prolift procedure. While it is laudable that they were able to achieve better results than others, such outcomes can be attributed to their greater experience. Unfortunately, the other reports in the literature (including some of the early reports from the TVM group itself) demonstrate conclusively that these favorable results cannot be reliably reproduced at other sites and even less so with individuals in private practice who do not report their results in the literature. As discussed more fully in other sections of this report, results from specialists at academic centers (where publishing is an important professional activity) represent the "best case" scenario in terms of both positive and negative outcomes, whereas clinicians in private practice do not necessarily specialize in pelvic reconstructive surgery and are not usually equipped to systematically collect their patients' outcomes. As discussed below, patients with complications are particularly likely to seek care from clinicians other than the operating surgeons, leaving the operating surgeons with a skewed perspective as to the balance of patients doing well versus doing poorly.

In addition, in contrast to most articles that report mesh exposure occurring in relatively close proximity to the Prolift mesh implantation surgery, this article reported mesh exposure occurring at a median of 13 months after the index surgery. This emphasizes the fact that implantation of permanent synthetic Prolift mesh confers a LIFE-LONG risk of mesh-related complications. As discussed previously, the cumulative frequency of mesh-related complications will only increase with time.

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D. Post-launch Articles and Studies

Following the launch of the Prolift product and procedure, additional studies have been published and have yielded data further demonstrating the deficiencies of the Prolift product and procedure.

Clave et al[615]

Mesh explants from patients with complications after vaginal prolapse surgery including exposure, infection, and/or shrinkage were studied with histology, scanning electron microscope analysis, chemical analysis, Fourier transform infrared spectroscopy, and differential scanning calorimetry. Mesh explants consisted of different materials, including polypropylene monofilament meshes (Gynemesh PS mesh in the Prolift Systems is a low-density,

[615] ETH.MESH.02184940: Clave A et al. Polypropylene as a reinforcement in pelvic surgery is not inert: comparative analysis of 100 explants. Int Urogynecol J 2010; 21: 261-270.

monofilament, polypropylene mesh). Histologic analysis revealed three types of reactions: type 1, characteristic of infection; type 2, chronic inflammation, and type 3, sclerosis and fibrosis. Polypropylene monofilament explants showed all three types of reactions and were more frequently associated with sclerosis compared with the other mesh types. In meshes implanted for at least 3 months, electron microscopy showed degradation, as evidenced by surface peeling, cracks with disintegrated surfaces and partially detached material, and superficial or deep flaking. Over 21% of low-density polypropylene monofilament mesh explants showed degradation.

The Conclusion stated, in part, that "This study, however, brings in to question the prevailing understanding of PP [polypropylene] as inert when used in vaginal surgery for pelvic floor repair procedures. In this work, not all types of PP implants degraded equally. The PP implants degraded more in the presence of an acute infection or chronic inflammation." The authors also summarized some of the unique conditions of vaginal prolapse surgery that enhance polypropylene degradation, including fatty acid diffusion into the mesh from "the massive accumulation of blood-derived fatty acids" caused by the extensive dissection and frequent hematomas in mesh-based prolapse surgery; and radical oxidation due to the septic environment of acute infections, bacterial contamination and colonization, and chronic inflammation.

These findings directly contradict Ethicon's claim about the *in vivo* performance of Gynemesh PS mesh in the Prolift Systems, including that implantation of Gynemesh PS mesh elicits a transient and minimum to slight inflammatory reaction, followed by deposition of a thin fibrous layer of tissue; that the mesh remains soft and pliable; that normal wound healing is not impaired; and that the mesh is not subject to degradation or weakening by the action of tissue enzymes.[616] These results and others clearly demonstrate that implantation of Gynemesh PS mesh elicits a chronic and severe inflammatory reaction, followed by pronounced sclerosis and fibrosis; that the mesh is encased in mature collagen, causing vaginal stiffness; that wound healing is distinctly impaired, as shown by the frequency of mesh exposure and other mesh-related complications; and that the mesh is subject to substantial degradation by mechanisms including fatty acid diffusion and radical oxidation. Ethicon merely copied the Performance text from previous mesh products and assumed without any testing that Gynemesh PS mesh would behave in exactly the same way in vaginal prolapse surgery as in animal studies.[617]

The Ultrasound Articles

[616] ETH.MESH.02341526

[617] ETH.MESH.01160159, Gynemesh Prolene Soft mesh, pre-clinical functionality testing strategy, 11-1-2001, Histology: "… This product [polypropylene] is not subject to degradation over time. Based on the results of animal testing performed on Prolene sutures and mesh, it is expected that initially following surgical placement of Gynemesh Prolene Soft mesh there will be a transient slight inflammatory reaction. A thin layer of fibrous connective tissue will then cover the mesh and penetrate the interstices. The clinical tissue compatibility of Gynemesh Prolene Soft mesh is essentially equivalent to Prolene mesh since the Gynemesh Prolene Soft mesh is chemically unchanged from Prolene mesh and sutures." Conclusion: "Based upon the Gynemesh Prolene Soft mesh's product characteristics, intended clinical indications and the use of existing polymer materials, additional pre-clinical functionality testing is not required."

An important body of literature recognizes the utility of ultrasounds to identify polypropylene mesh in the female pelvis and document objective evidence of mesh contraction/shrinkage/retraction.

As noted above in the section discussing mesh use in hernia repair, mesh contraction has been consistently observed, ranging from 20% to 50%. More recent articles demonstrate the same phenomenon when polypropylene mesh is used in vaginal prolapse surgery. Of critical importance, ultrasound studies of mesh implants after vaginal prolapse surgery also identify significant folding of the mesh implants that accounts for a varying degree of the decreased length or surface area of the mesh implants.

In a 2007 study,[618] anterior and posterior Prolift mesh implants decreased in length by 35% to 39%, leaving 50% or more of the vaginal length unsupported by mesh. The authors described that "The wavy appearance and thickening of the mesh on sonography supports the possibility that there is concertina-like folding of the mesh in vivo."

In a 2008 study,[619] Perigee mesh implants measured an average of 21 ± 7 mm at a range of 2 to 24 months after surgery. Although the authors did not have comparative measurements to calculate the degree of mesh shrinkage by percentage or area, the Discussion stated that their data were in agreement with Tunn et al[620] who found substantial loss of the initial length of the mesh implant. In addition, the authors described that the "…ultrasound findings seem to suggest a varying degree of intra- or postoperative folding of the mesh …"

One 2011 study[621] found mesh length decreased from 90.3 mm at surgery to 57.1 mm on the 4th postoperative day, which was interpreted by the authors as mesh folding. The mesh implant size decreased further to 48.3 mm at 3 to 5 months after surgery, which was interpreted as mesh shrinkage. Therefore, this study found an overall 43% reduction in mesh area by 3 to 5 months after surgery, with early mesh folding accounting for 38% of the reduction and later mesh shrinkage accounting for the remaining 15% of the reduction.

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[618] PLTMEDLIT-01252 (cited in ETH-02326): Tunn R, Picot A, Marschke J, Gauruder-Burmester A. Sonomorphological evaluation of polypropylene mesh implants after vaginal mesh repair in women with cystocele or rectocele. Ultrasound Obstet Gynecol 2007; 29: 449-452. Epub 1 March 2007.

[619] PLTMEDLIT-01247 (cited in ETH-02314): Shek KL, Dietz HP, Rane A, Balakrishnan S. Transobturator mesh for cystocele repair: a short- to medium-term follow-up using 3D/4D ultrasound. Ultrasound Obstet Gynecol 2008; 32: 82-86. Epub 10 June 2008.

[620] PLTMEDLIT-01252 (cited in ETH-02326): Tunn R, Picot A, Marschke J, Gauruder-Burmester A. Sonomorphological evaluation of polypropylene mesh implants after vaginal mesh repair in women with cystocele or rectocele. Ultrasound Obstet Gynecol 2007; 29: 449-452. Epub 1 March 2007.

[621] Svabik K et al. Ultrasound appearances after mesh implantation – evidence of mesh contraction or folding? Int Urogynecol J 2011; 22: 529-533.

Only one study claimed to find no evidence of mesh contraction.[622] Studying the Perigee system (American Medical Systems), the authors measured mesh size beginning at a minimum of 3 months after surgery and compared the findings in the same women up to a maximum of 52 months after surgery. The authors found that midsagittal mesh length increased slightly (from 32.7 to 35.8 mm) and coronal mesh diameter did not change (36.6 to 37.4 mm).

However, using data provided in the article, mesh contraction did in fact occur between the time of operation and the first measurement at 3 months after surgery. The original mesh implant had an area of 18.5 cm^2; at follow-up, the mesh implant had an average area of 12.0 cm^2. This represents a 35% decrease in mesh implant area by 3 months.

In the Discussion, the authors state that "… it is implausible that biological processes should change appearances so much within a few weeks. …" However, this statement is directly contradicted by voluminous evidence in the medical literature that such biological processes (healing and scarring) do indeed change the appearance and size of mesh implants within only a few weeks.

The first author, HP Dietz, reported financial conflicts of interest (as a consultant and paid speaker) with American Medical Systems that markets the Perigee System under study in this article. Of interest, in a 2008 study in which Dietz was a co-author that identified no conflicts of interest, financial or otherwise, the authors came to the opposite conclusion, that mesh contracted significantly (discussed above).[623]

Blandon et al[624]

The authors reported a case series of 21 patients referred for severe complications from mesh placement in vaginal prolapse surgery. More than half the patients had already undergone more than one procedure before referral in an attempt to address persistent signs and symptoms. Complications included mesh erosion in 12 women, dyspareunia in 10, and recurrent prolapse in 9; many patients had more than one complication. Despite that fact that the majority of these patients required even further surgical management, half of the sexually active patients still had refractory dyspareunia after surgery. The authors, surgeons at the Mayo Clinic, stated early in the article:

> We and others have observed an increasing number of complications, including complex mesh erosions, pain syndromes, recurrent prolapse, and dyspareunia, related to procedures using vaginally placed mesh to treat pelvic organ prolapse.

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[622] Dietz HP, Erdmann M, Shek KL (2011) Mesh contraction: myth or reality? Am J Obstet Gynecol 204 (173):e1–e4

[623] PLTMEDLIT-01247 (cited in ETH-02314): Shek KL, Dietz HP, Rane A, Balakrishnan S. Transobturator mesh for cystocele repair: a short- to medium-term follow-up using 3D/4D ultrasound. Ultrasound Obstet Gynecol 2008; 32: 82-86. Epub 10 June 2008.

[624] ETH-76750: Blandon RE et al. Complications from vaginally placed mesh in pelvic reconstructive surgery. Int Urogynecol J 2009; 20: 523-531. Epub Feb 10 2009

After describing their experience, the authors analyzed the situation:

One of our most important findings is that only 14% of patients were referred by the original surgeon, which suggests a lack of awareness of these complications by the original treating physician and the potential for under-reporting of the rate and extent of these complications due to nonrespondent/volunteer bias. Moreover, a urogynecologist was the original surgeon in only 9% of the cases. This supports the notion that surgical technique may contribute to the development of these complications and emphasizes the need for specialized training.

As a major referral center, we continue to observe an increasing number of patients presenting to our practice for evaluation and management of similar complications. With the growing popularity of mesh insertion kits, in which a large surface area of synthetic material is placed, the vaginal surgeon is faced with the challenges of very complex surgical dissections. If mesh excision is warranted, tissue fibrosis, scarring, bleeding, and urinary tract and anorectal injury are easily encountered, which add to patient morbidity. In our experience, if dyspareunia and pain syndromes are the main complication and if palpable contractions and scarring are noted throughout the vagina, we favor the complete excision of the body of vaginal mesh, leaving the "arms" in place.

…

It is important to remember that a percentage of patients who undergo pelvic reconstructive surgery with vaginally placed mesh will have life-changing complications. Moreover, whereas minor complications such as small vaginal mesh erosions are simple and easy to manage, incapacitating pelvic pain, dyspareunia, and large-scale erosions can be exceedingly complex and not easily resolved.

…

However, we support the notion that the new minimally invasive total mesh repairs should be done in the context of clinical trials, in which patients receive adequate informed consent and outcomes are carefully monitored. When complications arise, multiple surgeries to address them may be required; substantial morbidity may ensue, and the patient's quality of life may be greatly affected. **The widespread marketing of these technologies should be avoided until level I evidence becomes available demonstrating their superiority over traditional repairs, with acceptable rates of morbidity.**

The questions of what degree of training is sufficient and who should be performing these types of procedures remain highly debated. We have developed an ongoing registry to prospectively collect data on these affected patients. In addition, the creation of a more optimally used national database should be established to allow patients and providers the opportunity to report mesh-related complications. This, along with data from ongoing trials, will begin to provide the necessary data to adequately study the mechanisms that contribute to efficacy and affect morbidity. Practitioners are

compelled to answer these questions for the integrity of our profession as well as for the benefit of our patients.

Abbott, et al., Evaluation and management of complications from synthetic mesh after pelvic reconstructive surgery: a multicenter study, Am J Obstet Gynecol 2014; 210:163.e1-8, also addressed the severe complications and difficult treatment that results from mesh kits including the Prolift. This article was authored by physicians with a great deal of experience with the use of mesh kits and treatment of the complications. The complications and issues discussed in the article apply to the Prolift. Foremost, they found that TVM patients, "had a significantly higher occurrence of pelvic pain, dyspareunia, vaginal spotting, vaginal constriction, and obstructed defecation…" (e5). As in the Blandon article, above, the authors here recognized that the original implanters likely are not aware of the full scope of complications suffered by their patients since the patients self-refer to others for treatment of mesh complications in many cases. (e6). The article also recognizes the highest severity of complications is with TVM, and that the complications are, "more chronic in nature, and can be more difficult to treat," including, "mesh erosion, pelvic pain, dyspareunia, vaginal constriction, vaginal spotting, and obstructive defecation," and that the majority of these patients required more than one surgical treatment for their complications. (e6).

Mesh (non-Prolift) Randomized Trials

Sivaslioglu et al[625]

In this study, 90 patients were randomly assigned to either site-specific anterior repair or mesh repair for primary anterior vaginal prolapse. In the anterior colporrhaphy group, 40 patients underwent site-specific cystocele repair with absorbable suture (polyglactin 910, Vicryl); 3 patients, paravaginal defect repair; and 2 patients, cystocele and paravaginal defect repair. In the mesh group, 45 patients underwent placement of polypropylene mesh (Sofradim, Parietene) with transobturator passage of 2 arms on each side. The authors did not describe the study population by stage of prolapse at baseline; all patients were having primary repair.

At a mean of 12 months (range, 8-16 months), 42 patients in the site-specific anterior repair group and 43 patients in the mesh group had follow-up. Recurrent prolapse, defined as ICS POPQ $\geq$ stage II in the anterior vagina, occurred in 28% (12 of 42) in the site-specific anterior repair group versus 9% (4 of 43) in the mesh group. Patients in both groups experienced similar improvements in quality-of-life scores.

Mesh erosion occurred in 3 of 43 patients (7.0%), and all were treated with excision. New dyspareunia developed in 2 of 43 patients (4.6%) in the mesh group versus none in site-specific anterior repair group. Urinary retention occurred in 1 patient in the mesh group. New stress

[625] Sivaslioglu AA et al. A randomized comparison of polypropylene mesh surgery with site-specific surgery in the treatment of cystocele. Int Urogynecol J 2008; 19: 467-471. Online September 28, 2007.

incontinence developed in 3 of 42 patients (7.1%) in the site-specific anterior repair group versus none in mesh group, although treatment was not stated. No mesh shrinkage was observed. Reoperation in either group was not reported.

Although the authors stated in the Discussion that "long-term results should be [a]waited," no further report on this study population was found by PubMed search.

Unfortunately, 2 major aspects of study design directly affect the validity of the results. First, the authors chose to perform site-specific anterior repair rather than traditional anterior colporrhaphy. In randomized trials comparing site-specific versus traditional colporrhaphy, recurrent prolapse judged by anatomic criteria occurred more frequently after site-specific surgery (22%-33%) than traditional colporrhaphy (14%).[626] Therefore, the higher failure rate for the site-specific procedure chosen by the authors may not represent the most effective choice of traditional vaginal prolapse surgery as a comparison with transvaginal mesh prolapse surgery.

Second, the study population included women with significant apical prolapse that was not specifically addressed by the site-specific anterior repair. Although entry criteria excluded women with concomitant rectocele or enterocele, uterine or vaginal vault prolapse was not specifically excluded. At baseline in both groups, POPQ point C (representing the cervix) was at a relatively low level, at a mean of -2 cm (above the hymen) in the mesh group and -2.7 cm in the site-specific anterior repair group. Several studies have confirmed the substantial contribution of apical prolapse to the appearance of anterior vaginal prolapse.[627] Therefore, it seems likely in this study that apical prolapse was undiagnosed and unaddressed, contributing at least in part to the apparent anatomic failure in the site-specific anterior repair group.

There were no disclosures of financial conflicts of interest.

The Hiltunen Series

Hiltunen et al published 3 articles on the same study population with varying lengths of follow-up. The first article reported 1-year follow-up;[628] the second reported follow-up of

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[626] Abramov Y et al. Site-specific rectocele repair compared with standard posterior colporrhaphy. Obstet Gynecol 2005; 105: 314-318.
Paraiso MF et al. Rectocele repair: a randomized trial of three surgical techniques including graft augmentation. Am J Obstet Gynecol 2006; 195: 1762-1771.

[627] Summers A et al. The relationship between anterior and apical compartment support. Am J Obstet Gynecol 2006; 194: 1438-1443.
Hsu Y et al. Anterior vaginal wall length and degree of anterior compartment prolapse seen on dynamic MRI. Int Urogynecol J 2008; 19: 137-142. Epub 2007 June 20.
Lowder JL et al. The role of apical vaginal support in the appearance of anterior and posterior vaginal prolapse. Obstet Gynecol 2008; 111: 152-157.

[628] ETH-60188: Hiltunen R et al. Low-weight polypropylene mesh for anterior vaginal wall prolapse: a randomized controlled trial. Obstet Gynecol 2007; 110 (2 Pt 2): 455-462.

approximately 2 years;[629] and the third reported 3-year follow-up.[630] The original study population consisted of 96 women randomly assigned to the vaginal surgery group (anterior colporrhaphy) and 104 women to the mesh group (nonabsorbable low-weight monofilament polypropylene [Parietene, Sofradim] placed over the anterior colporrhaphy stitches with 4 arms extending toward the retropubic space and ischial spines). Most patients had primary prolapse (only 22% with previous prolapse or incontinence surgery), and more than one-third (36%) had stage II prolapse at baseline.

Recurrent prolapse as an anatomic outcome was defined as ≥ ICS POPQ stage II. By the definition of anatomic outcome, recurrent prolapse was more common in the mesh group than the non-mesh group. However, the level of recurrent prolapse in the non-mesh group remained stable over time, while the level of recurrent prolapse in the mesh group nearly doubled from 1 year to 3 years of follow-up. In the non-mesh group, recurrent prolapse occurred in 38.5% at 1 year, 41% at 2 years, and 41% at 3 years. In the mesh group, recurrent prolapse occurred in 6.7% at 1 year, 11% at 2 years, and 13% at 3 years.

At each point of follow-up, no difference in symptom resolution existed between the 2 groups. Although results at 1 year indicated a higher level of persistent and new stress incontinence in the mesh group (23%) versus the non-mesh group (10%), this difference did not persist at 2 and 3 years of follow-up, presumably due to intervening treatment of stress incontinence. By 3 years of follow-up, the frequency of reoperation was higher in the mesh group. In the non-mesh group, 17 of 96 patients (18%) underwent surgery for stress incontinence (n=9) or prolapse repair (n=8). In the mesh group, 25 of 104 patients (24%) underwent surgery, 14 for mesh exposure and 11 for stress incontinence (n=5) or prolapse repair (n=6).

Unfortunately, the study did not assess health-related or prolapse-specific quality of life and assessed symptoms of prolapse using a non-validated questionnaire (in the Discussion, the authors explained that validated questionnaires were not available in the Finnish language). Symptoms were assessed on an ordinal scale, ranging from 1 to 5. However, answers corresponding to “never” or “not at all” were scored as 1, rather than anchoring the scale at zero for the absence of symptoms. This has the effect of artificially inflating the mean scores by at least a value of 1. In addition, by using a non-validated questionnaire, the authors were unable to determine what constituted a clinically significant difference in scores and relied only on statistically significant differences. For example, at 2 years of follow-up, the authors reported a statistically significant difference in scores related to the sensation of vaginal bulging, with the score of 1.4 ± 0.8 in the non-mesh group versus 1.2 ± 0.5 in the mesh group (P = .02). With the artificial inflation of scores from the zero anchor to 1 and standard deviations of 0.5 to 0.8, a difference in the mean scores of only 0.2 is not likely to represent a clinically significant difference. In addition, in the articles reporting 1-year and 3-year follow-up, the proportion of

[629] ETH-76654: Nieminen K et al. Symptom resolution and sexual function after anterior vaginal wall repair with or without polypropylene mesh. Int Urogynecol J 2008; 19: 1611-1616. Epub 21 Aug 2008.
[630] PLTMEDLIT01406: Nieminen K et al. Outcomes after anterior vaginal wall repair with mesh: a randomized controlled trial with a 3 year follow-up. Am J Obstet Gynecol 2010 (3): 235.e1-8. Epub 2010 May 21.

patients experiencing the sensation of vaginal bulge was reported instead of the mean score, and there was no difference between the 2 groups.

The authors reported no financial conflicts of interest to disclose; the studies were supported by hospital research funds.

Nguyen and Burchette[631]

In this study, 38 women were randomly assigned to anterior colporrhaphy and 37 women, to Perigee polypropylene mesh repair, along with other prolapse or incontinence procedures as needed. Most patients (81%) had primary prolapse, and over half (55%) had stage II anterior vaginal prolapse at baseline.

After follow-up of 1 year, recurrent anterior prolapse (defined as ICS POPQ ≥ stage II) occurred in 45% of the anterior colporrhaphy group and 13% of the Perigee group. Patients with recurrent prolapse were not symptomatic. Both groups experienced similar levels of improvement in symptoms and quality of life, based on short-form PFDI and PFIQ questionnaires. There was no difference in sexual function scores between the 2 groups.

One patient in the anterior colporrhaphy group underwent Burch colposuspension and paravaginal repair for stress incontinence and stage II anterior vaginal prolapse 15 months after the index surgery. Two patients in the Perigee group had vaginal mesh exposure, treated with estrogen and in-office excision.

In the Discussion, the authors expressed great concern regarding the unknown long-term effects of permanent mesh and, because of the long-term durability and safety of mesh-reinforced repair is unknown, suggested that mesh repairs be restricted to procedures for recurrent prolapse or primary repairs with a high risk of recurrence.[632] Although the authors described this report as a 1-year interim analysis of the study, no further report on this study population was found by PubMed search.

There were no author disclosures of financial conflict of interest; the study was supported by an unrestricted educational grant from American Medical Systems, makers of Perigee.

[631] Nguyen JN, Burchette RJ. Outcome after anterior vaginal prolapse repair: a randomized controlled trial. Obstet Gynecol 2008; 111: 891-898.

[632] Nguyen JN, Burchette RJ. Outcome after anterior vaginal prolapse repair: a randomized controlled trial. Obstet Gynecol 2008; 111: 891-898. "The long-term disposition of permanent mesh is of great concern. …" "Because the long-term durability and safety of mesh-reinforced repair is unknown, surgeons may consider using these procedures for recurrent prolapse or primary repairs in cases where there is a high risk of recurrence and after discussion of risks, benefits, and alternatives."

Natale et al[633]

In this study, patients were randomly assigned to Gynemesh PS mesh (n=96) versus Pelvicol porcine dermis implant (n=94) for recurrent anterior vaginal prolapse. Both implants were cut in an identical shape and positioned under the bladder with 2 arms in the periurethral tissue. In addition, all patients underwent high levator myorrhaphy for apical vaginal support. At 2-year follow-up, objective failure, defined as ICS POPQ ≥ stage II anterior vaginal prolapse, occurred in 28.1% of the Gynemesh PS group and 43.6% of the Pelvicol group.

Symptomatic improvement was similar in both groups, although vaginal bulging as a specific symptom of prolapse was not assessed. Sexual function assessed by PISQ-12 improved in the Pelvicol group and was unchanged in the Gynemesh PS group. New dyspareunia was not reported; the overall number of women reporting dyspareunia from before to after surgery decreased in both groups. New stress incontinence developed in 2 patients in the Gynemesh PS group and 1 patient in the Pelvicol group.

Mesh erosions occurred in 6.3% of the Gynemesh PS group, all treated with excision, versus none in the Pelvicol group. Other than mesh excision, no reoperations occurred.

In the Discussion, the authors referred to the need for risk-benefit assessment when choosing graft augmentation of prolapse repair, given mesh-related complications such as erosion and dyspareunia.[634]

The study was performed independently of corporate assistance. The authors reported no conflicts of interest.

Carey et al[635]

In this study, 139 patients with anterior and posterior vaginal prolapse were randomly assigned to anterior and posterior colporrhaphy versus central anterior and posterior plication with overlay of Gynemesh PS mesh. Anterior mesh placement was performed with a cross-shaped implant with mesh arms in the paravaginal space abutting the pubic bone. Posterior mesh placement was performed with a Y-shaped implant with mesh extensions abutting the sacrospinous ligament. Additional procedures included sacrospinous ligament fixation in 47% of the colporrhaphy group and 58% of the Gynemesh PS mesh group, and laparoscopic suture

[633] ETH-76690: Natale F et al. A prospective randomized controlled study comparing Gynemesh, a synthetic mesh, and Pelvicol, a biologic graft, in the surgical treatment of recurrent cystocele. Int Urogynecol J 2009; 20: 75-81. Epub 16 Oct 2008.
[634] ETH-76690. Discussion: "Although surgery with graft augmentation has been suggested as a way of yielding superior anatomic outcomes, this must be balanced against potential mesh-related complications such as erosion and dyspareunia."
[635] ETH-76774: Carey M et al. Vaginal repair with mesh versus colporrhaphy for prolapse: a randomized controlled trial. BJOG 2009; 116: 1380-1386. Epub 7 July 2009.

sacral hysteropexy in 5 patients in the colporrhaphy group and 2 patients in the Gynemesh PS mesh group.

Failure was defined as ≥ stage II prolapse at any vaginal site at 12-month follow-up. Failure was not statistically significantly different between the 2 groups, with 34.4% (21 of 61) in the colporrhaphy group versus 19% (12 of 63) in the Gynemesh PS mesh group. When patients lost to follow-up were imputed as failures, failure in the colporrhaphy group (42.9%) was statistically significantly higher (*P*=.049) than in the Gynemesh PS mesh group (26.1%). However, when patients lost to follow-up were imputed as successes, again no statistically significant difference was seen between the 2 groups, with 30% failure in the colporrhaphy group versus 17.4% in the Gynemesh PS group. Both groups experienced high levels of satisfaction, and improved symptoms and quality of life with no difference between the 2 groups.

Although no statistically significant differences at baseline were observed in the 2 groups, twice as many patients in the colporrhaphy group had previous prolapse surgery (26.2%) compared with the Gynemesh PS mesh group (13.6%). Since this would bias the colporrhaphy group to a higher failure rate, the lack of difference in postoperative anatomic and functional outcomes between the groups becomes even more significant.

Serious intraoperative complications were uncommon, with 1 bladder and 1 bowel injury, both repaired at the index surgery without sequelae, in the colporrhaphy group, and 1 hemorrhage in the Gynemesh PS mesh group. Mesh exposure occurred in 4 patients (5.6%) in the Gynemesh PS group and was treated surgically in 3 patients. Four patients in the colporrhaphy group had subsequent surgery, 2 for prolapse and 2 for vaginal stenosis.

The first author has a consulting agreement with Ethicon involving the paid evaluation of new products, and Ethicon provided a study grant and the Gynemesh PS mesh product for the study.

Prolift Randomized Trials

The Iglesia series

Iglesia et al published 2 articles on the same study population with varying lengths of follow-up. The first article reported minimum 3-month follow-up and median follow-up of 9.7 months (range, .24-26.7 months);[636] and the second reported minimum 1-year follow-up and mean follow-up of 14.7 months.[637] The original study population consisted of 65 women with multi-compartment prolapse, 33 randomly assigned to the vaginal surgery group (most commonly treated with uterosacral ligament suspension, anterior and/or posterior colporrhaphy)

[636] Iglesia CB, Sokol AI, Sokol ER, Kudish BI, Gutman RE, Peterson JL, Shott S. Vaginal mesh for prolapse: a randomized controlled trial. Obstet Gynecol 2010; 116: 293-303.
[637] Sokol AI et al. One-year objective and functional outcomes of a randomized clinical trial of vaginal mesh for prolapse. Am J Obstet Gynecol 2012; 206: 86.e1-9.

and 32 women to the Prolift group (treated with anterior, posterior, or total Prolift). For patient safety, study enrollment was halted when the predetermined threshold of 15% Prolift mesh exposure was exceeded. Previous surgery for prolapse had been performed in only 4 of 65 women (6%); baseline prolapse was stage II in 11 of 65 patients (17%).

Recurrent prolapse as an anatomic outcome was defined as ≥ ICS POPQ stage II. By the definition of anatomic outcome, recurrent prolapse was no different in the non-mesh group compared to the Prolift group, despite longer follow-up in the non-mesh group (mean 16.2 ± 5.4 months) versus the Prolift group (mean 13.2 ± 4.7 months). In the non-mesh group, recurrent prolapse occurred in 70.4% at early follow-up and 69.7% at later follow-up. In the Prolift group, recurrent prolapse occurred in 59.4% at early follow-up and 62.5% at later follow-up. However, no patients in the non-mesh group required reoperation for prolapse, and 3 of 32 patients (9%) in the Prolift group had reoperation for recurrent prolapse.

Complications occurred more commonly in the Prolift group, including mesh exposure in 5 patients (15.6%). At later follow-up, 5 patients in the Prolift group required 6 operations, compared with none in the non-mesh group. In the Prolift group, 2 patients (6%) had intraoperative cystotomy and repair.

At each point of follow-up, no difference in symptom resolution existed between the 2 groups. The study assessed quality of life and symptoms using validated questionnaires and found no difference between the 2 groups. There was no difference in the proportion of patients with subjective cure of vaginal bulge symptoms between the non-mesh group (90%) and the Prolift group (96.2%).

Ethicon was involved with this study by providing the Prolift kits and providing feedback on the manuscript before publication. The authors reported no conflicts of interest.

The publication of the Iglesia et al article prompted 2 letters to the editor, both letters from individuals closely allied to Ethicon's financial interests in promoting Prolift. Of interest, the wording in both letters closely matches wording in Ethicon's response to the FDA regarding the Iglesia et al article (see below for further discussion). One letter criticized the study methodology by stating that the required minimum surgeons' experience of 10 vaginal mesh procedures was "hardly enough cases to obtain expertise in the transvaginal mesh procedure."[638] The authors responded, in part, that "Our trial was conducted by surgeons who were fellowship-trained, with expertise in all routes of reconstructive pelvic surgery, and who represent the skilled surgeons to whom new technology is often marketed" and that "If expert surgeons from multiple institutions cannot get the outcomes of a few individuals, perhaps there is something wrong with the procedure."[639] The other letter criticized the predetermined threshold of 15%

[638] Lucente VR. Vaginal mesh for prolapse: a randomized controlled trial [letter]. Obstet Gynecol 2010; 116: 1456-1457.
[639] Iglesia CB et al. Vaginal mesh for prolapse: a randomized controlled trial [reply]. Obstet Gynecol 2010; 116: 1457.

Prolift mesh erosion for halting study enrollment.[640] The authors responded, in part, that "… this protocol was devised, and interim analyses were conducted, due to concerns for potential adverse events and patient safety."[641]

These articles, Iglesia et al reporting 3-month follow-up and Sokol et al reporting 1-year follow-up, received considerable attention, both within and outside of Ethicon.[642] Shortly after the publication of the Iglesia et al article, Ethicon held a meeting to consider the study's results and concluded that there was "no need for corrective and/or preventive actions" because the 15.6% Prolift mesh erosion rate in the Iglesia et al article fell within the range (3.2-19.3%) in the Prolift Clinical Expert Report.[643] However, Ethicon never updated the Prolift IFU to adequately inform physicians about the expected frequency of Prolift mesh erosion, and Ethicon never updated any of its marketing materials directed at physicians and patients to reflect the expected frequency of Prolift mesh erosion. Before FDA review, Prolift patient brochures described the risk of Prolift mesh exposure as "small." After FDA review, Prolift patient brochures didn't describe the risk of Prolift mesh exposure in any way, qualitative or quantitative, despite the FDA's request that Prolift mesh exposure be described as "one of the most common adverse events" after the Prolift procedure.[644]

In addition, the FDA requested that Ethicon provide a response to them after publication of the Iglesia et al article. Ethicon interacted closely with one of the principal authors (Dr. Sokol) of the article in planning its response to the FDA.[645] Despite this, Ethicon intentionally withheld information provided by Dr. Sokol in their response to the FDA, instead distorting the truth and responding to the FDA in misleading and inaccurate ways.[646] Ethicon claimed that the article did not represent Level I evidence, based on the fact that the study was underpowered. This is a specious argument; Ethicon knew well that the study did not enroll its planned sample size when enrollment was halted for patient safety after reaching the predetermined threshold of 15% Prolift mesh erosion. Ethicon even criticized the study design for establishing such a threshold, based on an earlier study that reported mesh erosion in 17.3%, which again emphasizes Ethicon's disregard for the paramount importance of patient safety. Ethicon questioned the definition of erosion in 1 case, as if terming the event as "incomplete wound healing" instead of Prolift mesh erosion would change the nature of the complication for the patient.

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[640] Jacquetin B et al. Vaginal mesh for prolapse: a randomized controlled trial [letter]. Obstet Gynecol 2010; 116: 1457-1458.
[641] Iglesia CB et al. Vaginal mesh for prolapse: a randomized controlled trial [reply]. Obstet Gynecol 2010; 116: 1458.
[642] Reuter's Health, 7-28-2010, http://www.thedoctorschannel.com/view/mesh-support-for-vaginal-prolapse-repair-prone-to-erosion-2/ (ETH.MESH.00311250)
Reuter's Health, 9-9-2011, http://www.thedoctorschannel.com/view/jury-still-out-on-value-of-mesh-in-vaginal-prolapse-repair/
11-4-2011, http://commonhealth.wbur.org/2011/11/surgery-under-scrutiny-what-went-wrong-with-vaginal-mesh
[643] ETH.MESH.00310834
[644] ETH-01322-01323
[645] ETH.MESH.00598420
[646] ETH.MESH.02252792

Ethicon challenged the authors' technique used to place the synthetic Prolift mesh, based on 1 case in which a surgeon attached the deep anterior mesh arms to the sacrospinous ligament to enhance apical support.[647] Ethicon ignored information from Dr. Sokol that this modification occurred in only 1 case and then told the FDA that this occurred "in an unspecified number of cases."[648] Ethicon criticized the study methodology that required surgeons' experience of at least 30 vaginal colpopexy procedures and 10 vaginal mesh procedures. It is truly mind-boggling that Ethicon would dare to criticize a surgeon's experience of 10 vaginal mesh procedures, when Ethicon knew well that surgeons could obtain their certificate of training and operate on unsuspecting patients without ever performing a single Prolift procedure beforehand. Furthermore, Ethicon only required a minimum experience of 3 Prolift procedures before their preceptors began teaching other surgeons how to perform Prolift.[649] In the context of this trial design, Ethicon again ignored information from Dr. Sokol that emphasized that the requirement for 10 vaginal mesh procedures was "the MINIMUM required," that "most surgeons had performed well more than this minimum number," and that "mesh procedures were being performed outside the study protocol during the same period."[650] Ethicon withheld this information from the FDA, as if this was a legitimate study criticism.

Although Ethicon claimed to the FDA that "A significant body of evidence favoring the use of mesh grafts in urogenital prolapse surgery over traditional repairs has been published," Ethicon cited 10 articles (not included in the reference list and 1 citation could not be found at all), none of which studied Prolift specifically. Ethicon cited 2 more articles that did study Prolift, both with authors reporting financial conflicts of interest due to Ethicon support and both published in 2011. One study reported no difference in subjective outcomes and mesh erosion in 16.9%.[651] The other study reported somewhat better outcomes for anterior Prolift versus anterior colporrhaphy, with substantially increased complications in the Prolift group, including intraoperative visceral injury and hemorrhage, reoperation rate, new stress incontinence, dyspareunia, and pain.[652] (See below for further discussion of these articles.) Furthermore, the Iglesia et al article was published in July 2010 and Ethicon corresponded with Dr. Sokol in August 2010, yet Ethicon did not respond to the FDA's request until May 17, 2011, suggesting that Ethicon delayed its response to the FDA until after the 2 articles cited above were published (February and May 2011, respectively).

The Altman RCT[653]

[647] ETH.MESH.00598422
[648] ETH.MESH.02252794
[649] ETH.MESH.00129582
[650] ETH.MESH.00598422
[651] Withagen MI et al. Trocar-guided mesh compared with conventional vaginal repair in recurrent prolapse. Obstet Gynecol 2011; 117: 242-250.
[652] Altman D et al. Anterior colporrhaphy versus transvaginal mesh for pelvic-organ prolapse. N Engl J Med 2011; 364: 1826–1836.
[653] Altman D et al. Anterior colporrhaphy versus transvaginal mesh for pelvic-organ prolapse. N Engl J Med 2011; 364: 1826–1836.

Altman et al published a randomized clinical trial comparing anterior colporrhaphy in 189 patients to the anterior Prolift procedure in 200 patients with 1-year follow-up. The primary outcome was defined as a composite of prolapse at ICS stage 0 or I and no symptoms of vaginal bulging. At 1 year, 60.8% of the Prolift group met the criteria for success, compared with 34.5% of the anterior colporrhaphy group. The Prolift group also had better results when the primary outcome was evaluated separately by its 2 components, prolapse stage and symptom of vaginal bulging. For prolapse at ICS stage 0 or I, 82.3% of the Prolift group versus 47.5% of the anterior colporrhaphy group met this criterion. For no symptom of vaginal bulging, 75.4% of the Prolift group versus 62.1% of the anterior colporrhaphy group met this criterion.

Weighing against the better prolapse outcomes in short-term follow-up, however, the Prolift group experienced more intraoperative and postoperative complications, including a higher frequency of reoperation after only 1 year. Reoperation was necessary in 13 patients (6.5%) in the Prolift group versus 1 patient (0.5%) in the anterior colporrhaphy group. For the index surgery, general anesthesia was required more often in the Prolift group (41.5%) than the anterior colporrhaphy group (30.7%). Average operative time was almost twice as long in the Prolift group (52.6 minutes) compared to the anterior colporrhaphy group (33.5 minutes), despite Ethicon's claims to the contrary in marketing to patients.[654] Hemorrhage (defined as > 500 mL) occurred in 5 patients (2.5%) in the Prolift group, compared with none in the anterior colporrhaphy group. Bladder injury occurred in 7 patients (3.5%) in the Prolift group versus 1 patient (0.5%) in the anterior colporrhaphy group. Voiding difficulties were more common in the Prolift group (in hospital, 8% and requiring catheterization within 2 months in 2.5%) compared to the anterior colporrhaphy group (in hospital, 3.2% and requiring catheterization within 2 months in 1.1%). New stress incontinence was twice as likely in the Prolift group (12.3%) as in the anterior colporrhaphy group (6.2%). Pain with sexual intercourse was almost 4 times higher in the Prolift group (7.3%) compared to the anterior colporrhaphy group (2%). Pain was experienced more frequently in the Prolift group (inguinal pain in hospital, 2.5%; severe pelvic pain at 2 months, 2.5%; and severe pelvic pain at 1 year in 0.5%) versus in the anterior colporrhaphy group (no inguinal pain in hospital, severe pelvic pain at 2 months, 0.5%; and no severe pelvic pain at 1 year).

Other than dyspareunia, which was more common in the Prolift group as noted above, sexual function measured by the PISQ-12 did not differ between the 2 groups. Condition-specific health-related quality of life was measured with the Urogenital Distress Inventory (UDI), and the UDI summary score showed no difference between the 2 groups.

The majority (84%) of patients in the study population were undergoing primary repair of prolapse. About half (52%) had an early stage of prolapse (stage II, within 1 cm of the hymen); indeed, only 84% of patients experienced the symptom of vaginal bulging before surgery. Given current recommendations from several professional organizations, including ACOG/AUGS and

[654] ETH-01267, Prolift patient brochure: "It [Prolift] can be completed in less than half the time of traditional surgery."

SGS,[655] patients with early stage prolapse undergoing primary repair are not good candidates for transvaginal mesh surgery because of the excess risk.

Unfortunately, the long-term risks of vaginal mesh implantation are not fully known, although it is known that the risks are life-long. The authors cautioned that "Patients should understand, however, that the use of mesh may cause complications even after the immediate postoperative period." Almost one-quarter (24%) of the Prolift group was aged 32 to 58 years, comprising women who can be expected to live for another 30 to 50 years with the ongoing risk of Prolift mesh complications. The authors concluded that "When one is counseling patients regarding surgical options, the benefits of the mesh kit must be balanced against the higher rates of surgical complications and postoperative adverse events associated with this approach."

Ethicon provided partial support for this study. In addition, two authors, Altman and Falconer, have been identified in previous studies as having advisory positions with Gynecare Scandinavia, a company associated with Ethicon and within the family of Johnson & Johnson companies.

Further Analysis of the Altman Study

I. Substantial Ethicon Input into the Altman et al Article Published in the New England Journal of Medicine

Based on my review of Ethicon documents related to the Altman randomized trial and article reporting the primary outcomes, Ethicon provided substantial input to Altman on key aspects of study design, data analysis and interpretation, and preparation of the manuscript before submission, despite a clear statement in the draft manuscripts and published article that denied any such involvement. Thus, the article misled the reviewers, editors, and readers of this article as if the content of the article had been prepared without the biased influence of the Prolift manufacturer, when this was clearly not the case.

In the Methods section of the Altman et al article, the authors claimed that "The manufacturer of the mesh kit did not provide the products used in this trial and had no involvement in the study design, data collection and analysis, the writing of the manuscript, or the decision to submit the results for publication."[656]

However, this claim is untrue.

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[655] Vaginal placement of synthetic mesh for pelvic organ prolapse. Committee Opinion No. 513. American College of Obstetricians and Gynecologists. Obstet Gynecol 2011; 118: 1459-1464.
Society of Gynecologic Surgeons (SGS) Executive Committee Statement Regarding the FDA Communication: Surgical placement of mesh to repair pelvic organ prolapse imposes risks, 7-25-2011.

[656] Altman D et al. Anterior colporrhaphy versus transvaginal mesh for pelvic-organ prolapse. N Engl J Med 2011; 364: 1826–1836.

The authors failed to disclose the nature and extent of Ethicon's involvement with this study, thereby misleading the reviewers, editors, and readers of this article into the mistaken belief that the study's results were presented in an unbiased way, free from the influence of the mesh kit's manufacturer. In direct contradiction to the authors' claim denying Ethicon's involvement, Ethicon had substantial input into the study's data analysis and writing of the manuscript. In fact, Altman enthusiastically thanked Ethicon for its "efforts," stating that "I think the manuscript really improved based on your comments."[657]

In addition, the Ethicon employees who provided substantial input into the study's data analysis and writing of the manuscript failed to correct the published article's statement that falsely claimed their lack of involvement. These Ethicon employees had several opportunities to correct the false statement, which was present in the draft versions of the manuscript that they reviewed. Moreover, Ethicon failed to correct the false claim in the pre-publication version of the article, received several days before actual publication. In this way, Ethicon was complicit in misleading the reviewers, editors, and readers of this article into falsely believing that data analysis and presentation of the study's results were not influenced by the well-known effect of industry and commercial bias. Such complicity defeats the purpose of making disclosures at all and places at risk not only the integrity of the data from this study, but also the integrity of the investigators who, knowingly or otherwise, supported such complicity. Full and accurate disclosures are critically important for reviewers, editors, and readers when interpreting the results of industry-sponsored studies. Ethicon's misrepresentation of its involvement served Ethicon's commercial interests, in maintaining a fiction of investigator and author independence while, at the same time, exerting strong pressure to manipulate the presentation of data regarding Prolift in the most favorable light.

In terms of data analysis, Ethicon's input determined which POPQ point was used in the definition of recurrent prolapse, which served as one of the two components of the composite primary outcome. Judith Gauld (Ethicon clinical affairs) informed Altman that "We use [POPQ point] Ba rather than Aa …" in defining prolapse outcomes. This is a critically important point that could have a substantial effect on the primary outcome of the study.

In terms of involvement in writing the manuscript, at least 4 Ethicon employees provided in-depth review and extensive commentary on several iterations of the manuscript before submission, including at least 3 reviews by Judith Gauld and at least 2 reviews each by 3 physicians in Ethicon medical affairs, David Robinson, Piet Hinoul, and Aaron Kirkemo. In addition, an unnamed Ethicon statistician apparently reviewed the manuscript as well, with comments input by Gauld. The comments from each individual were numbered and labeled with the individual's initials. Based on the documents that I have reviewed, it appears that Gauld reviewed an early version of the manuscript and tables, and she provided 24 comments during this review;[658] in another review of the tables and figure, Gauld provided 15 additional

[657] 8-19-2010, ETH.MESH.0426464: "I think the manuscript really improved based on your comments. Thank you so much for your efforts and continued support!"
[658] ETH.MESH.02991996; ETH.MESH.02992001; ETH.MESH.02992006

comments.[659] All 4 individuals reviewed a subsequent version of the manuscript.[660] Of a total of 72 comments made during that review, Gauld provided 20 comments; Robinson, 20 comments; Hinoul, 22 comments; and Kirkemo, 10 comments. On behalf of all 4 individuals, Gauld provided more commentary about presenting the data on sexual function.[661] Finally, Hinoul provided even more commentary about presenting the data on sexual function on behalf of all 4 individuals.[662] Therefore, the 4 (or 5) Ethicon employees provided Altman with a total of 119 specific comments for the draft manuscript.

Many other changes, often deletions and/or insertions of text, were not identified by the specific individual at Ethicon; those changes are not listed here. In total, among the draft documents that I reviewed, 69 changes of this nature were identified.

As detailed below, Ethicon's input had a substantial effect on the content of the manuscript before submission and therefore required accurate disclosure, rather than the inaccurate claim that Ethicon had no involvement in writing the manuscript. The effect of Ethicon's input was most obvious and egregious in relation to the presentation of data on sexual function and dysfunction. Specifically:

- Altman deleted from the abstract and the text the statement reporting a statistically significantly higher overall prevalence of dyspareunia in the Prolift group, which was described by Robinson as an "enormously high" number.
- Altman deleted from the abstract the statement reporting a higher prevalence of dyspareunia that occurred 'usually' or 'always' in the Prolift group.

Furthermore, Ethicon employees clearly expected that their input would result in the "suggested changes" despite disclaimers to the contrary and in direct contradiction of Hinoul's testimony. Ethicon exerted strong pressure to influence Altman to keep data on dyspareunia out of the abstract ("which will be the only thing most surgeons read" according to Hinoul) and preferably out of the manuscript altogether. In response, Altman was apologetic[663] but insistent that one sentence on dyspareunia be included in the text; no data at all on sexual function (or any other functional outcome, for that matter) were reported in the abstract. Nevertheless, Ethicon employees were clearly annoyed at Altman and expressed frustration at his "intransigence."[664]

Moreover, due to strongly worded objections from Ethicon, Altman deleted an entire paragraph in the Discussion section in which he described a series of research studies that would serve as a "model for introduction of new surgical devices" due to "the lenient regulatory oversight for invasive medical devices when compared to drugs." Both Robinson and Hinoul strongly objected

[659] ETH.MESH.04526470-74; 78; 79
[660] ETH.MESH.01757713
[661] ETH.MESH.04526475
[662] ETH.MESH.00578946
[663] ETH.MESH. 04526466: "I'm sorry to be so pig-headed on this matter and I don't want you to get the impression that I don't care about your comments. I do, and most of your suggested revisions will be performed. …"
[664] ETH.MESH.00578943

to this, claiming that such a system would "call a halt to innovation" in Hinoul's words. In the final article, Altman deleted the entire substance of this paragraph.

Ethicon Input on Prolapse Data Analysis

Results: Table 1, Baseline Characteristics of the 389 Patients Entering the Study, Draft manuscript:

> Footnote defining POPQ stages that were used as part of the primary outcome: "POP-Q stages defined as: stage II point Aa -1 cm proximal to the hymen to 1 cm distal of the hymen; stage III point Aa more than 2 cm distal to the hymen but less than the total vaginal length; stage IV point Aa equals the total vaginal length i.e. complete vaginal eversion."

Gauld comment:

> "We use Ba rather than Aa as it is considered the leading edge, whereas Aa is a fixed point between -3cm and 3cm."

Final article:

> Footnote defining POPQ stages that were used as part of the primary outcome: "In stage 2 of the Pelvic Organ Prolapse Quantification (POP-Q) system, the anterior vaginal wall (adjacent to the bladder) descends to at least 1 cm above the hymen but not more than 1 cm below it; in stage 3, the anterior vaginal wall descends more than 1 cm below the hymen but less than the total length of the vagina."

Ethicon Input on Presentation of Sexual Function Data

Abstract, Draft manuscript:

> "The rate of dyspareunia was 34% in the colporrhaphy group compared to 51% in the mesh group (P=0.02)."

Kirkemo comment:

> "Needs clarification. Is this de novo, persistent, or both?"

Robinson comment:

> "Presumably this is post op? These are enormously high numbers that will require detailed explanation."

Final article:

> DELETED: "The rate of dyspareunia was 34% in the colporrhaphy group compared to 51% in the mesh group (P=0.02)."

Results, Patient-Reported Outcomes, Draft manuscript:

> "When considering dyspareunia in specific ('Do you feel pain during sexual intercourse?'), the proportion of women reporting having dyspareunia was 46/101 (34%) in the colporrhaphy group compared to 68/110 (51%) in the mesh group (P=0.02)."

Gauld comment:

> "The baseline data to this specific question are not included in table 5. I think it important to know if the groups were well balanced at baseline re dyspareunia."

Robinson comment:

"Is there no baseline data on dyspareunia? Do we know how many became sex active post op who were not preop for each group? Did any dyspareunia cases require reintervention? In the mesh group, how many of the dyspareunia patients had exposure? Did the dyspareunia resolve after fixing the exposure problem?"

Final manuscript:

DELETED: "When considering dyspareunia in specific ('Do you feel pain during sexual intercourse?'), the proportion of women reporting having dyspareunia was 46/101 (34%) in the colporrhaphy group compared to 68/110 (51%) in the mesh group (P=0.02)."

Results, Patient-Reported Outcomes, Draft manuscript:

"In the colporrhaphy group, dyspareunia was reported present 'usually' or 'always' in 2/101 patients (2.0%) compared to 8/110 (7.3%) patients in the mesh group (P=0.07)."

Gauld comment:

"How many of these were de novo compared to ongoing from baseline?"

Final article:

"… pain during sexual intercourse was reported to occur 'usually' or 'always' by 2% of women after colporrhaphy and by 7.3% after transvaginal mesh surgery (P=0.07)."

Results, Patient-Reported Outcomes, Draft manuscript:

"There was, however, no significant difference between the groups with regard to overall satisfaction with sexual life ('Overall, how satisfied are you with your sexual relationship with your partner?') with 37/92 (40%) in the colporrhaphy group, and 51/106 in the mesh group (48%) responding 'usually' or 'always' (P=0.37)."

Gauld comment:

"Due to the lack of specificity to this question, I'm not sure it worth including here."

Final article:

"When the patients were asked how satisfied they were with their sexual relationships with their partners, 40% of the colporrhaphy group and 48% of the mesh-repair group answered 'usually' or 'always' (P=0.37)."

NOTE: In contrast to Gauld's original opinion on presenting sexual satisfaction data, by the time of Ethicon's last review of Altman's manuscript, Ethicon advocated for the presentation of sexual satisfaction data, in order to "show a completely different impression" of sexual function after Prolift, in contrast to the dyspareunia data that was significantly worse after Prolift than after colporrhaphy.

Gauld on behalf of Ethicon:[665]

"… we would suggest that for the purposes of this paper that only the overall PISQ-12 data are presented as pre-defined in the protocol, and state in this current manuscript that

[665] ETH.MESH.04526475

detailed analysis and interpretation of the individual questions will be reported in a separate paper.

"For the question 5 data to be clinically meaningful in terms of a suitable measure of dyspareunia, we would suggest pre-defining what responses were considered to constitute dyspareunia, such as needing a response of always or usually to q 5 – otherwise, the criteria for dyspareunia is pretty broad ranging from seldom to always. Perhaps this is something that could be considered for the future sexual function paper. Moreover, the key piece to the dyspareunia results are whether the symptoms are de novo, so if you do include in this paper, we would recommend that the data were presented in this way."

Hinoul on behalf of Ethicon:[666]

"Thank you for giving us a last chance to have a look at this before submission. Of course we respect the fact that this is, and must remain, an independent study. Overall the team feels that the sexuality part of the manuscript still lacks accuracy.

The abstract, which will be the only thing most surgeons read, states: "Dyspareunia was present usually or always in 2/101 patients (2.0%) after colporrhaphy compared to 8/110 (7.3%) patients in the mesh group (P=0.07)." As this was not really one of the clearly predefined endpoints, we feel that reporting on the PISQ score would be more scientifically appropriate. For example: "The PISQ-12 scores, were similar for both arms of the study (35.1 (33.7-36.4) versus 35.0 (33.7-36.4 (p=0.99)."

We feel that selecting one reported outcome somehow will be used by the mesh antagonists, whilst you may just as well have selected overall sexual satisfaction to go in the manuscript which would show a completely different impression "overall satisfaction with sexual life ('Overall, how satisfied are you with your sexual relationship with your partner?') with 37/92 (40%) in the colporrhaphy group, and 51/106 in the mesh group (48%), responding 'usually' or 'always' (P=0.37)." (This is probably reflected in the fact that the improvement in PISQ is overall larger after Prolift vs colporrhaphy as baseline PISQ scores were 33.1 versus 32.2)"

<u>Ethicon Input on Discussion of Evaluating Invasive Medical Devices</u>

Discussion, Draft manuscript:

"As such, our results highlight the need for a thorough evaluation of surgical innovations before market release. The present trial was the final step of an international multicenter collaboration initiated to evaluate the use of a mesh kit for pelvic organ prolapse repair. We designed a study program extending over five years to investigate perioperative morbidity in a cross-sectional study, safety and subjective outcomes in a cohort study, and finally the mesh kit effectiveness in a randomized comparison with current treatment

[666] ETH.MESH.00578946

standard. Given the lenient regulatory oversight for invasive medical devices when compared to drugs, this approach could serve as a future model for introduction of new surgical devices which resembles the three phase programs required before bringing prescribed pharmaceuticals to market."

Robinson comment:

"Daniel, this obviously is your call but the ability of industry to deliver any innovation if your model was used would be non-existent. Collection of such data may be done over the life of the device but there must be some return on investment in order to support that degree of research."

Hinoul comment:

"Daniel, I completely agree with Dave [Robinson]. It would call a halt to innovation. I would not call it 'introduction.' I would refer to it as 'general use outside of clinical trials' or 'before novel treatment modalities can be considered standard of care.'"

Final article:

"Our results highlight the need for a careful evaluation of surgical innovations, which are often widely adopted in the absence of data from clinical trials."

DELETED: "The present trial was the final step of an international multicenter collaboration initiated to evaluate the use of a mesh kit for pelvic organ prolapse repair. We designed a study program extending over five years to investigate perioperative morbidity in a cross-sectional study, safety and subjective outcomes in a cohort study, and finally the mesh kit effectiveness in a randomized comparison with current treatment standard. Given the lenient regulatory oversight for invasive medical devices when compared to drugs, this approach could serve as a future model for introduction of new surgical devices which resembles the three phase programs required before bringing prescribed pharmaceuticals to market."

<u>Other Comments</u>

Abstract, Draft manuscript:

"At the 12 month assessment, an optimal outcome was significantly more common in the transvaginal mesh group compared to the colporrhaphy group (60% vs. 36%, P<0.001)."

Gauld comment:

"Not consistent with results presented in Table 1."

Final article:

"At 1 year, the primary outcome was significantly more common in the women treated with transvaginal mesh repair (60.8%) than in those who underwent colporrhaphy (34.5%) …"

Introduction, Draft manuscript:

"In the US alone, more than 300,000 surgical procedures for pelvic organ prolapse are performed each year. {Popovic, 2001 #2511]"

Gauld comment from 1st review:

"I'm not familiar with this, and couldn't find it. I would tend to use Shah et al – from 2008 – blue journal."

Gauld comment from 2nd review:

"Suggest consider citing Shah, who reported 2003 data, Int Urogynecol J (2008) 19: 421-428."

Final article:

Same sentence with 2001 Popovic citation deleted and added citation to: Shaw AD et al. The age distribution, rates, and types of surgery for pelvic organ prolapse in the U.S. Int Urogynecol J 2008; 19: 421-428.

Introduction, Draft manuscript:

"Given the high rates of recurrence after surgical treatment of pelvic organ prolapse, innovation and development of surgical techniques are called for."

Hinoul comment:

"Maybe you want to state that the traditional techniques using endogenous tissues show a high recurrence rate and that exploring innovative concepts that may lead to improved outcomes are called for."

Final article:

"However, because the risk of recurrence is 40% or more with this procedure [anterior colporrhaphy], there has been great interest in innovative surgical techniques that may improve outcomes after cystocele repair."

Introduction, Draft manuscript:

"… to compare the mesh kit with standard treatment."

Hinoul comment:

"With the current standard of care?"

Final article:

"… to determine the efficacy and safety of transvaginal mesh repair for prolapse of the anterior vaginal wall, as compared with the current standard of care."

Methods: Study Design, Draft manuscript:

"… patients were included if they … presented with symptomatic primary or recurrent prolapse …"

Gauld comment:

"Was this [referring to 'symptomatic'] characterized further such as using the UDI question on bulge?"

Final article:

"Patients were invited to participate if they … presented with primary or recurrent prolapse … and with symptoms of vaginal bulging or pelvic heaviness."

Methods: Study Design, Draft manuscript:

"… patient-reported outcomes of urogenital symptoms, sexual function, and impact on daily activities."

Hinoul comment:

Regarding "impact on daily activities," "How did you measure this?"

Final article:

DELETED: "impact on daily activities"

Methods: Surgical Procedures, Draft manuscript:

"… trocar guided transvaginal procedure using the PROLIFT®-system (Ethicon, Somerville, NJ)."

Gauld comment:

"This is the correct checked against the trademark list" in reference to corrections that Gauld made to the naming of the Prolift product.

Final article:

"… use of the Gynecare Prolift Anterior Pelvic Floor Repair System kit (Ethicon)."

Methods: Surgical Procedures, Draft manuscript:

"All participating surgeons had instructor supervised hands-on training before study start and performed the procedure independently before study initiation."

Kirkemo comment:

"Was there a minimum experience in order to participate?"

Final article:

"All surgeons were qualified to perform both interventions."

Methods: Statistical Analysis, Draft manuscript:

"Based on previous studies, …" [referring to sample size calculation]

Gauld comment:

"Need to add references."

Final article:

"On the basis of a previous study, …" and cited to Elmer C et al. Trocar-guided transvaginal mesh repair of pelvic organ prolapse. Obstet Gynecol 2009; 113: 117-126.

Methods: Statistical Analysis, Draft manuscript:

"Primary analysis used the intention-to-treat principle …"

Gauld comment:

"Our statistician commented that this is not correct as it doesn't include the 21 patients randomized but not treated. Instead, he suggests using the term Full Analysis Set."

Robinson comment:

"I may not understand the concept but how is this ITT [intention to treat] if only observed outcomes are analyzed?"

Final article:

"The primary analysis used the full data set, …"

Results: Study Population, Draft manuscript:

No information about enrollment across sites.

Gauld comment:

"May be worth describing range of enrolment across the sites – ie was there a big difference or was it well balanced?"

Final article:

"The 58 surgeons who participated in the trial performed a median of 3 of each of the two types of procedures (range, 1 to 8 for the mesh repair and 1 to 9 for colporrhaphy)."

Results: Complications and Morbidity, Draft manuscript:

"Non-adherence to treatment assignment was low and similar for the treatment groups: 3.7% for colporrhaphy versus 4.5% for transvaginal mesh (P=0.69)."

Gauld comment:

"This sentence belongs in the first section entitled study population. Also, suggest that a comment is added whether these were inadvertent mis-randomisations or some other rationale?"

Final article:

Results, Study Population: "Rates of nonadherence to the treatment assignment were low and were similar in the two treatment groups (3.7% for the colporrhaphy group and 4.5% for the mesh-repair group, P=0.80)."

Results: Patient-Reported Outcomes, Draft Manuscript:

"When considering the prolapse specific terms 'Do you experience heaviness in the pelvic area?', 21/174 (12.1%) patients in the colporrhaphy group compared to 7/180 (3.9%) patients in the mesh group experienced symptoms (P=0.007), and for 'Do you experience a feeling of bulging or protrusion in the vaginal area?' the corresponding figures were 31/174 (17.8%) in the colporrhaphy group versus 9/179 (5.0%) in the mesh group (P<0.001)."

Gauld comment:

"Suggest inclusion in Table 3 so that the two components of making up the optimal outcome are both included rather than just the anatomy."

Final article:

"In secondary analyses performed to assess the two components of the primary outcome separately, use of the transvaginal mesh kit was superior to colporrhaphy with regard to … the percentage of those who had symptoms of vaginal bulging (75.4% vs. 62.1%, P=0.008) at 1 year (Table 2)."

NOTE: Note the dramatic change from the draft manuscript to the final article in the proportion of patients who experienced the symptom of vaginal bulging in both groups, which suggests changes in the definition of a key component of the primary outcome.

Results: Adverse Events, Draft manuscript:

> "Other postoperative complications were of similar frequency in the two treatment groups (Table 5)."

Robinson comment:

> "I don't understand how there can be a stat sig diff [statistically significant difference] in antibiotic prophylaxis and vag [vaginal] tamponade if the protocol required such for both arms."

Final article:

> DELETED: Reporting of antibiotic prophylaxis and use of vaginal tamponade (packing).

NOTE: This raises a substantial concern about the likelihood of other protocol violations, measured and unmeasured, that could affect the study's outcomes. Rather than addressing this issue, Altman simply deleted the data reporting these protocol violations.

Results: Adverse Events, Draft manuscript:

> "Furthermore, a total of 5 patients in the mesh group complained of pelvic pain or discomfort at two months follow-up, compared to 1 in the colporrhaphy group; all cases but one had resolved spontaneously at the one year visit."

Robinson comment:

> "Was this a mesh case?"

Final article:

> "Five patients in the mesh-repair group reported severe pelvic pain at 2 months as compared with one patient in the colporrhaphy group (P=0.22); in all except one of these patients (who was in the mesh-repair group), the pain had resolved spontaneously by the 1-year follow-up visit."

Results: Adverse Events, Draft manuscript:

> "… 6 patients (3.2%) underwent vaginal surgery due to mesh exposure (excision and or covering of the mesh) …"

Robinson comment:

> "We should understand whether covering the mesh resolved the problem as I am not sure I ever saw a case were [sic] this was successful."

Final article:

> "… and 6 (3.2%) had undergone vaginal wound revision (in all cases to correct mesh exposure) (P=0.03)."

Results: Table 1, Baseline Characteristics of the 389 Patients Entering the Study, Draft manuscript:

Inclusion of UDI, IIQ-7, and PISQ-12 scores.

Gauld comment:

"I would be inclined not to include any patient reported outcomes in this table – see comment in table 5."

Final article:

Inclusion of total UDI score, UDI subscores, and PISQ-12 score.

Results: Table 1, Baseline Characteristics of the 389 Patients Entering the Study, Draft manuscript:

Presentation of POPQ as stage II and stage III-IV.

Gauld comment from 1st review:

"Suggest that this be broken out for stages III and IV?"

Gauld comment from 2nd review:

"Suggest that this is broken down to breakout III and IV separately"

Final article:

Presentation of POPQ as stage II and stage III (ie, no patients with stage IV).

Results: Table 1, Baseline Characteristics of the 389 Patients Entering the Study, Draft manuscript:

Title of table referring to "389 Patients Entering the Study"

Gauld comment:

"Not sure that this is correct definition – perhaps should state in full analysis set or ITT [intention-to-treat] (see other comments)"

Final article:

Title of table refers to "389 Study Patients"

Results: Table 1, Baseline Characteristics of the 389 Patients Entering the Study, Draft manuscript:

Row title under column headed "Characteristic": "Cesarean deliveries"

Gauld comment:

"Should this state number of patients who had c-section?"

Final article:

Data on cesarean deliveries reported by number of patients.

Results: Table 1, Baseline Characteristics of the 389 Patients Entering the Study, Draft manuscript:

Footnote describing responses to UDI and PISQ-12.

Gauld comment from 1st review:

"Although stated in the methods, suggest pointing out here that 48 is best score for PISQ-12 and 300 is worst for UDI."

Gauld comment from 2nd review:

"Again, suggest separating this to state 300 is worst score for UDI and 48 is best score for PISQ-12."

Final article:

Separate footnotes for UDI and PISQ-12.

"Scores on the Urogenital Distress Inventory (UDI) range from 0 to 300, with higher scores indicating greater distress (or 'bother')."

"Scores on the short-form Pelvic Organ Prolapse/Urinary Incontinence Sexual Questionnaire (PISQ-12) range from 0 to 48, with higher scores indicating better sexual function."

Results: Table 3, Surgical Outcome after Colporrhaphy Versus Transvaginal Mesh, Draft manuscript:

Success versus failure at 2 months and 1 year presented for optimal outcome and anterior vagina at POP-Q stages 0-1

Gauld comment from 1st review:

"Suggest consideration of including the subjective success rates here as well – so that the components (anatomy and sensation of bulge) making up the optimal outcomes are both included."

Gauld comment from 2nd review:

"In addition to the separate anatomic data, suggest including the bulge data in this table"

Final article:

Table 2, Primary and Secondary Outcome Measures after Colporrhaphy versus Mesh Repair for Anterior Vaginal Wall Prolapse, including composite primary outcome, anterior prolapse stage 0 or 1, and symptoms of vaginal bulge

Results: Table 2, Surgical Outcome After Colporrhaphy Versus Transvaginal Mesh, Draft manuscript:

Data in row describing success at 1 year

Gauld comment:

"This is not consistent with the abstract."

Final article:

Results consistently reported in the abstract and table.

Results: Table 3, Odds of Optimal Surgical Outcome in Relation to Baseline Characteristics One Year After Surgery, Draft manuscript:

Variables: "No previous pelvic floor surgery" and "Previous hysterectomy"

Gauld comment:

"Should this read 'no prior hysterectomy'?"

Final article:

Heading of “Previous hysterectomy” with “No” and “Yes” below

Results: Table 4, Patient Reported Outcomes After Colporrhaphy Versus Transvaginal Mesh, Draft manuscript:

Column headings for colporrhaphy and transvaginal mesh

Gauld comment:

“Suggest adding n numbers.”

Final article:

Column headings for Colporrhaphy Group and Mesh-Repair Group followed by number of patients (N).

Results: Table 5, Surgical Characteristics for the Colporrhaphy and Transvaginal Mesh Group, Draft manuscript:

Under heading of Anesthesia, “Generell”

Gauld comment:

“Sp – General”

Final article:

Data on type of anesthesia not presented.

Results: Figure representing participant enrollment, randomization, and follow-up, Draft manuscript:

“412 underwent randomization” with reasons for 21 patients who did not enter study

Gauld comment:

“21 pts randomised but not treated – need to describe the split between mesh and traditional repair.”

Final article:

The reasons for not entering the study for 15 patients in colporrhaphy group and 6 patients in Prolift group were described separately.

Discussion

Draft manuscript:

“… and largely insensitive to as-treated analysis and disadvantageous imputation of missing data.”

Hinoul comment:

Regarding “as-treated analysis,” “I wonder whether this is a generally accepted term.”

Final article:

“… and persisted even after the imputation of missing data to the disadvantage of the mesh kit.”

Discussion
Draft manuscript:

> "However, compared to incontinence surgery, observational studies agree that the use of synthetic mesh for pelvic organ prolapse surgery is associated with higher rates of late complications. Undesirable properties of polypropylene mesh in situ are well described and include exposure, contraction, and rejection, which may trigger symptoms such as groin and pelvic pain or discomfort. By adopting precautionary measures such as antibiotic prophylaxis, pre- and postoperative topical estrogen treatment of menopausal women, and a tension-free surgical technique, mesh related adverse events can be reduced but never completely avoided. Additional surgery to address mesh related adverse events was reported in 3% of our study population which is in the lower range of previously reported complication rates in relation to the use of mesh kits. The continuing occurrence of mesh related complications does, however, require surgeons who implement trocar guided transvaginal mesh into clinical practice to manage complications extending beyond the immediate postoperative period."

Robinson comment:

> "Should this be 'may' instead of 'can' since I am not sure there is proof of such. Also, what about hydrodissection?"
>
> > NOTE: The surgical procedure for anterior Prolift mesh implantation, described in the supplemental appendix, did not describe hydrodissection.

Final article:

> "Surgery to address mesh complications was reported in 3% of the women randomly assigned to the mesh procedure. This is higher than the complication rates reported after the use of midurethral sling procedures for incontinence but lower than in another study of the use of transvaginal mesh for prolapse surgery. Although the study populations may not be directly comparable, the low rate of mesh complications in our trial may be attributed at least in part to the antibiotic prophylaxis and local estrogen therapy provided to the patients and the supervised training sessions for all participating surgeons. Patients should understand, however, that the use of mesh may cause complications even after the immediate postoperative period."
>
> DELETED: "Undesirable properties of polypropylene mesh in situ are well described and include exposure, contraction, and rejection, which may trigger symptoms such as groin and pelvic pain or discomfort."

Discussion
Draft manuscript:

> "Use of validated quantification systems for prolapse grading and subjective outcomes minimized classification bias."

Robinson comment:

> "Was there any POPQ training for the investigators? What was their level of familiarity with the system? We have encountered significant issues with lack of consensus in other POP studies we have done."

Final article:

DELETED: "Use of validated quantification systems for prolapse grading and subjective outcomes minimized classification bias."

Discussion

Hinoul comment:

"Should you discuss anything about the patient selection? As it is a purely anterior wall study, can we say anything about the apical support, which in the US is still a hot item. I believe that you prove with correct patient selection you have an excellent repair."

Final article:

ADDED: "Although the vaginal apex is often involved in large cystoceles, anterior mesh kits are not intended to suspend the vaginal apex but rather to support the anterior vaginal wall. The apparent lack of effect of apical descensus on the outcomes after cystocele repair may reflect the small number of patients in our trial who had clinically significant prolapse of the upper vagina and should be interpreted with caution."

<u>Additional comments that apparently did not result in direct changes to the manuscript:</u>

Robinson comments:

- Methods, Surgical Procedures: "I think either the name of the suture or its loss of tensile strength information should be included" in reference to the description of the anterior colporrhaphy procedure.
- Results, Study Population: "Is this one of the places to state how many mesh patients underwent further surgery for exposures?" in reference to the statement as to how many patients had the index surgery for recurrent prolapse.

  NOTE: Hinoul responded "I would say no, Dave."
- Results, Patient Reported Outcomes: "Do you believe this is related to recurrent prolapse in the colporrhaphy group which then prevented the unmasking of SUI at 1 year?" in reference to the increased prevalence of stress incontinence in the Prolift group.
- Discussion: "Is this difference [more stress incontinence in mesh group] seen because colporrhaphy technique allowed periurethral sutures where Prolift does not treat the urethra or bladder neck?"

  NOTE: The surgical procedure for anterior colporrhaphy, described in the supplemental appendix, did not include periurethral sutures.
- Discussion: "This sentence is unclear, I believe. Do you mean that the degree of deterioration was the same in both groups or that the same pattern of greater deterioration in the colporrhaphy group was seen?" referring to the sentence stating "A similar pattern of deterioration was observed for anatomic outcomes."
- Discussion: "Either here or in the discussion of study strengths and weaknesses, I believe the lack of some very meaningful data collection regarding sex function/dyspareunia needs to be called out."

- Discussion: “Was this [intraoperative cystoscopy] not required by protocol for the mesh group?

  NOTE: In the supplemental appendix, under the heading of “Additional details on surgical procedures,” it is stated that use of cystoscopy was left to the discretion of the surgeon.
- Discussion: “Hence the cysto” made in regard to the statement in the draft manuscript “Bladder perforation is a potentially serious complication if unrecognized, but can often be managed without sequela if promptly identified and adequately repaired.”
- Discussion: “Do you want to again call out the identification of recurrence risk factors that may guide surgeons in the patient counseling?”

  NOTE: This is apparently in reference to a statement in the Results section of the draft manuscript that reported increased odds of treatment success for the transvaginal mesh kit versus anterior colporrhaphy associated with baseline characteristics of advancing age, normal body mass index, two or more childbirths, previous pelvic floor surgery, and recurrent anterior vaginal prolapse. However, in the final article, it was reported that none of the baseline characteristics showed significant interactions with either study treatment.

Hinoul comments:

- Abstract: “I miss the QOL data.”

  NOTE: This suggests that this draft manuscript is a later iteration and that Hinoul had already reviewed a prior version.
- Introduction: “Short term” made in regard to the term “tentative”
- Methods, Randomization: “Was the follow-up done by a physician blinded to the procedure that had been carried out?”
- Methods, Study Measures: “Should you specify?” made in regard to the statement in the draft manuscript “patient-reported outcomes of urogenital symptoms.”
- Methods, Surgical Procedures: “Aquadissection?” in reference to the description of the anterior Prolift procedure
- Methods, Surgical Procedures: “I believe the correct spelling to be: Colporrhaphy. I only correct/mention it here.”
- Methods, Surgical Procedures: “Agree with Dave, need suture size and material. Were they continuous or running sutures?” in reference to the description of the anterior colporrhaphy procedure.
- Methods, Statistical Analysis: “This is not clear to me either. Best to ask Pete’s or Bob’s advice, but reading further in the results it seems to overcome any criticism of possible bias” in reference to the planned sensitivity analysis.
- Methods, Statistical Analysis: “intervals do not overlap it is appropriate to conclude” in reference to the interpretation of confidence intervals.
- Results, Primary Outcome Measure: “What does this mean? Per protocol set?” in reference to the term “as-treated analysis.”

- Results, Complications and Adverse Events: “Should you mention transfusion and or specific management of the hemorrhage?” in reference to operative blood loss in the Prolift group.
- Discussion: “I believe this study [of urodynamic findings] is based on some of the patients included in this trial. I think you should state if that was a publication on a subanalysis of this study.”
- Discussion: “But you made sham incisions you state earlier in the M&M [Materials & Methods] section” made in regard to the statement in the draft manuscript “On the other hand, it would have been difficult to blind a trained examiner to surgical procedure since the trocar inguinal exit incisions are visible …”

  NOTE: At the time of anterior colporrhaphy, skin markings were made, not incisions.
- Discussion: “Anything about the short term outcome?”
- Discussion: “But what is your final recommendation now that you have done it?” made in regard to the last sentence in the Discussion section of the draft manuscript “Accruing clinical evidence of benefits from the use of mesh kits should not forestall efforts to continuously monitor already commercially available products to ensure patient safety.”

Kirkemo comments:

- Introduction: “Sounds like we are talking flex HD. Doesn’t he mean mesh? Seems a more specific term warranted” made in regard to the term “biomaterials”
- Methods, Randomization: “Were sham incisions made in the groin and perineum?”

  NOTE: At the time of anterior colporrhaphy, skin markings were made, not incisions.
- Methods, Statistical Analysis: “Is this appropriate? I would think that one would consider any LTFUs [losses to follow-up] as failures regardless” in reference to the planned sensitivity analysis.
- Results, Study Population: “Mesh or fascia or both?” in reference to the statement that none of the patients had previously pelvic reconstructive surgery using biomaterial implants.

  NOTE: Hinoul responded “I think they mean any kind of biocompatible graft.”
- Results, Complications and Adverse Events: “Did it preclude mesh placement, cause case abandonment or conversion to colporrhaphy?” in reference to bladder perforation in the Prolift group.
- Results, Complications and Adverse Events: “Was it associated with concomitant sling?” in reference to postoperative urinary tract infections and bladder emptying difficulties.

  NOTE: Per the study protocol, no concomitant surgery was performed in either treatment group.
- Discussion: “May want to stratify complications by numbers of cases and/or training” made in regard to the statement “However, the spectrum of complications associated with the use of trocar guided transvaginal mesh kits requires surgeon proficiency and adequate resources to cope with adverse events which may occur during, and in the aftermath, of surgery.”

Gauld comments from 1st review:

- Title page, 2 comments: "This should now state Ethicon Women's Health & Urology" in reference to Gynecare in the financial disclosure statement.
- Results, Table 2, Surgical Characteristics for the Colporrhaphy and Transvaginal Mesh Group: "I think these need some level of explanation in the text" in reference to "vaginal reoperation" for 2 patients in the mesh group under the heading of "Adverse events during hospital stay."
- Results, Table 5, Patient Reported Outcomes after Colporrhaphy versus Transvaginal Mesh: "May be worth considering a bar graph for presenting these data – and would suggest inclusion of the baseline values here as well to demonstrate the magnitude of effect."

Gauld comments from 2nd review:

- Methods, Study Design: "Suggest adding the extent of monitoring by the research nurse across the sites" in reference to the statement about the safety monitoring committee.
- Methods, Study Measures: "For both the UDI and PISQ-12, suggest that reference is made to translation into local languages and whether the translations were validated" in reference to identifying the patient-completed outcome measures.
- Methods, Study Measures: "Suggest that handling of missing data is included here – e.g. how were they classified in the event of missing response to question 16" in reference to the definition of the primary outcome of success.
- Methods, Study Measures: "Was this solely by PISQ-12, or were there additional questions asked?" in reference to statement about patient-reported outcomes of sexual function.
- Methods, Surgical Procedures: "Suggest some reference to training or agreement between investigators to adhere to an agreed surgical technique."
- Results: Table 3, Odds of Optimal Surgical Outcome in Relation to Baseline Characteristics One Year After Surgery: "Our statistician suggested a footnote to describe that the number of successes change when adjustments are made to the model." in reference to footnote stating "Denotes odds ratio with 95% confidence intervals."
- Results: Table 2, Surgical Outcome After Colporrhaphy Versus Transvaginal Mesh: "Suggestion from our statistician to add rows to describe 'missing/no data' and calculate the percentages out of the non-missing." in reference to footnote stating that "Columns not adding up to 100% represent missing values."
- Results: Table 3, Odds of Optimal Surgical Outcome in Relation to Baseline Characteristics One Year After Surgery: "Suggest that this row reflects those considered successes" in reference to row heading of "All patients"
- Results: Table 2, Surgical Outcome After Colporrhaphy Versus Transvaginal Mesh: In reference to the "absence of patient reported vaginal bulging" in the footnote defining optimal outcome, "Suggest adding the definition for this as well – q 16 of UDI"

ADDITIONAL NOTES

- In the supplementary appendix, the description of the anterior colporrhaphy procedure describes the suture material used only as "slow absorption monofilament thread," despite the fact that both Robinson and Hinoul suggested providing details about the exact suture type used, including the gauge. Given that this specific information was not provided, that suggests that suture material was not standardized for the anterior colporrhaphy procedure, which could have an impact on the likelihood of treatment success versus failure.
- In the supplementary appendix, the authors stated that sham incisions would be 2 cm wide, in explaining that ethical approval for sham incisions could not be obtained in all the participating sites. The surgical procedure for anterior Prolift mesh implantation does not state the size of the skin incisions made. The Prolift surgical technique document states that skin incisions should be 4 mm in length, not 2 cm.
- In the supplementary appendix, 2 tables are provided that represent the median and range of POPQ measurements. Table 1A provides the crude data before data cleaning, and Table 1B provides data used in the final analysis after incorrect POPQ values were omitted. The specific number of data points omitted was not provided.
- It is interesting that both Hinoul and Robinson ask about hydrodissection as part of the anterior Prolift procedure, in light of the fact that none of the Prolift IFUs mention hydrodissection, and the Prolift surgical technique guide does not mention hydrodissection by name, inaccurately describes infiltration of the vaginal wall rather than the vesicovaginal space, and describes this step as optional.
- It is interesting that Robinson seemed to expect that the surgical protocol would require cystoscopy to appropriately detect and manage intraoperative bladder injury, in light of the fact that the first and second Prolift IFUs and the Prolift surgical technique guide didn't even mention intraoperative cystoscopy during the Prolift procedure. The third Prolift IFU, available in October 2009, only suggested that cystoscopy could be performed, rather than recommending or requiring it. At no time did Ethicon provide the necessary guidance as to the appropriate timing of intraoperative cystoscopy.

Sequence of events related to submission of Altman manuscript:

Date	ETH number	Content	Comments
3-25-10	04526491	Email chain from Altman to Walker; Walker to Gauld; Gauld to Altman, copied to Walker	Request from Altman: "Is there someone at your office who would be able and willing to read the manuscript draft (the Prolift RCT) and professionally revise the English text?" Reply from Gauld: "I'd be very willing to help with this request below."
4-12-10	04526490	Email from Altman to Gauld, copied to Walker	Final manuscript delayed "… I hope that you are still willing to scrutinise the text."

Unknown	02991996	Results, discussion sections	Gauld review
Unknown	02992001	Tables	Gauld review
Unknown	02992006	Introduction, methods sections	Gauld review
Unknown	04526470	Tables	Gauld review
8-17-10	04526473	Figure	Gauld review
	04526478	Tables	Gauld review
8-11-10, 10:23	04526465	Email from Altman to Robinson, Walker, Gauld, and Hinoul with first version of manuscript	
8-17-10, 14:00	01757705	Email from Robinson to Altman, Walker, Gauld, Hinoul, and Kirkemo with feedback on the draft manuscript (01757713); tables (01757708); and figure (01757707)	"Thank you for allowing us to comment and please use our comments at your discretion."
8-17-10, 14:33	04526467	Email from Altman to Robinson, Walker, Gauld, Hinoul, and Kirkemo in response to feedback on manuscript	"Thank you all very much! This was exactly the kind of comments and critique I was hoping for. …" "You are asking for a lot of data on sexual function. It is impossible to include all data you are asking for in this manuscript due to limitations in the number of words. …"
8-17-10, 14:50	00518643	Email from Gauld to Robinson, Hinoul, Kirkemo, and Shen with draft response to Altman	Content as below
8-17-10, 16:02	04526475	Email from Gauld to Altman, copied to Robinson, Walker, Hinoul, and Kirkemo about sexual function data	"… we would suggest that for the purposes of this paper that only the overall PISQ-12 data are presented as pre-defined in the protocol, and state in this current manuscript that detailed analysis and interpretation of the individual questions will be reported in a separate paper. "For the question 5 data to be clinically meaningful in terms of a suitable measure of

			dyspareunia, we would suggest pre-defining what responses were considered to constitute dyspareunia, such as needing a response of always or usually to q 5 – otherwise, the criteria for dyspareunia is pretty broad ranging from seldom to always. Perhaps this is something that could be considered for the future sexual function paper. Moreover, the key piece to the dyspareunia results are whether the symptoms are de novo, so if you do include in this paper, we would recommend that the data were presented in this way. "One final comment is with regards to the IIQ-7 – the baseline data are presented but not the post-treatment results – it may be worth considering to include in Table 4?"
8-17-10, 17:40	04526466	Email from Altman to Gauld, copied to Robinson, Walker, Hinoul, and Kirkemo	"The problem is that the key question in everybodys mind when it comes to sexual function is the issue of dyspareunia, we all know that. Personally I think there is too much emphasis on this single issue at the expense of other important aspects of the female sexual response cycle. However, I know for sure that the paper will not be accepted unless we present some data on dyspareunia. Furthermore, it may seem as if we are trying to hide something if we don't present dyspareunia data. Thus, it will not suffice to give the overall PISQ scores only. "Unfortunately, there are no background studies exploring what should be considered normal sexual function according to PISQ, thus we have no cut-offs which we can refer to with regard to what constitutes dyspareunia or sexual dysfunction. Any arbitrary classification thus must be motivated by further analysis. Again, there simply is no more space left in the manuscript. We are close to 4500 words and have 5 large tables. What should I remove in order to make room for an expanded

			methods, results and discussion on sexual function? I will however take a closer look at the figures on de novo dyspareunia instead of the present overall figures. "I'm sorry to be so pig-headed on this matter and I don't want you to get the impression that I don't care about your comments. I do, and most of your suggested revisions will be performed. …"
8-19-10, 23:36	04526464	Email from Altman to Robinson, Walker, Gauld, Hinoul, Kirkemo with latest version of manuscript	
8-20-10, 14:57	04526463	Email from Altman to Barbara Walker	Manuscript submitted to NEJM
8-20-10, 16:13	00578946	Email from Hinoul on behalf of team to Altman	"Thank you for giving us a last chance to have a look at this before submission. Of course we respect the fact that this is, and must remain, an independent study. Overall the team feels that the sexuality part of the manuscript still lacks accuracy. The abstract, which will be the only thing most surgeons read, states: "Dyspareunia was present usually or always in 2/101 patients (2.0%) after colporrhaphy compared to 8/110 (7.3%) patients in the mesh group (P=0.07)." As this was not really one of the clearly predefined endpoints, we feel that reporting on the PISQ score would be more scientifically appropriate. For example: "The PISQ-12 scores, were similar for both arms of the study (35.1 (33.7-36.4) versus 35.0 (33.7-36.4 (p=0.99)." We feel that selecting one reported outcome somehow will be used by the mesh antagonists, whilst you may just as well have selected overall sexual satisfaction to go in the manuscript which would show a

			completely different impression "overall satisfaction with sexual life ('Overall, how satisfied are you with your sexual relationship with your partner?') with 37/92 (40%) in the colporrhaphy group, and 51/106 in the mesh group (48%), responding 'usually' or 'always' (P=0.37)." (This is probably reflected in the fact that the improvement in PISQ is overall larger after Prolift vs colporrhaphy as baseline PISQ scores were 33.1 versus 32.2)"
8-20-10, 13:51	00578943	Email from Altman to Hinoul, copied to Robinson, Gauld, Kirkemo	"I agree with you (!) but we have been painted into a corner by decades of focus on dyspareunia. I understand your concern and the reasons for your request. Again I think that the attention paid to dyspareunia is misguided at the expense of other important elements of female sexual function. "However, the first question a mesh antagonist will ask when looking at our outcomes is 'Well, that's fine, but what about dyspareunia??' I know this, because this is exactly what happened when we tried to publish our results from the prospective cohort study in two separate papers in the Green Journal to give a more accurate picture of the sexual function aspects. I had to fight really hard to keep the sexual function data outside the main publication. Unfortunately, I don't think we stand a chance to repeat that feat in NEJM, JAMA, Lancet or BMJ. If the paper ends up in a specialty journal, we will probably try and repeat the tactic of submitting the data as two connected articles (perhaps more): the first dealing with the main outcome measure and the second with sexual function." "The paper was submitted to NEJM this afternoon. …"

8-20-10, 19:57	00578943	Email from Kirkemo to Hinoul, copied to Robinson and Gauld	"Wow what intransigence. I thought you did a nice job talking about the placement of the PISQ in the abstract. As I read it, you didn't say anything about not mentioning dyspareunia."
8-20-10, 18:43	00578943	Email from Hinoul to Kirkemo, copied to Robinson and Gauld	"Breath in, breath out …"
8-20-10, 21:09	00578939	Email from Robinson to Hinoul and Kirkemo, copied to Gauld	"Breathe in, breathe out, move on."
8-20-10, 21:12	00578939	Email from Hinoul to Robinson	Winking smiley face emoticon

Depositions of Jeffrey M Drazen and Gregory D. Curfman

I also had the opportunity to review additional materials related to the article, "Anterior Colporrhaphy versus Transvaginal Mesh for Pelvic Organ Prolapse," authored by Dr. Daniel Altman et al. and published in the New England Journal of Medicine on May 12, 2011, with the correction subsequently published on January 24, 2013. These materials reviewed included deposition transcripts and exhibits of Drs. Jeffrey Drazen, editor-in-chief, and Gregory Curfman, executive editor of the New England Journal of Medicine.

The Altman article reported results from an Ethicon-sponsored Investigator Initiated Study, comparing outcomes of the Anterior Prolift System to anterior colporrhaphy in women with anterior vaginal prolapse. The originally published article claimed that "The manufacturer of the mesh kit did not provide the products used in this trial and had no involvement in the study design, data collection and analysis, the writing of the manuscript, or the decision to submit the results for publication." This claim was inaccurate, as clearly revealed by Ethicon policy with regard to their rights when sponsoring an Investigator Initiated Study; by documents detailing communications between Ethicon employees and Dr. Altman; and by sworn testimony from Ethicon employees.

After the editors of the New England Journal of Medicine became aware of the inaccuracy of the original claim regarding Ethicon's role in the Altman article, a correction was published that replaced the statement above and claimed that "As cosponsor of the trial, the manufacturer of the mesh kit reviewed the original study protocol and a presubmission draft of the manuscript. The manufacturer did not provide the products used in the trial and had no involvement in data collection and analysis or in the decision to submit the results for publication."

In my opinion, this statement, purported to correctly describe Ethicon's extent of involvement, was inadequate in failing to accurately reflect Ethicon's role in study protocol changes before sponsorship, in data analysis and interpretation, and in extensive participation in manuscript preparation that included several iterations of the draft manuscript before submission.

Another significant issue involved unreliable data collection for the primary outcome of the study. Anatomic outcomes were assessed using the Pelvic Organ Prolapse Quantification (POPQ) system. However, POPQ measurements in the originally published article included values outside the defined ranges, indicating that the measurements had been made and/or recorded in error. (The same problem has occurred in other Ethicon-sponsored studies.) These invalid measurements were simply excluded from analysis, and the authors never revealed how many errors occurred and whether the errors occurred more frequently in one of the two patient groups. After repeating analyses using a "cleaned" version of the POPQ data, the authors claimed that the results "were not materially different." However, without access to the crude and cleaned versions of the POPQ data, it is impossible to determine whether that claim is accurate or not.

These POPQ errors indicate a lack of basic knowledge as to how the POPQ examination and measurements are performed. Since the primary outcome measure relied on the POPQ values, the presence of these POPQ errors rendered the reported rate of recurrent prolapse unreliable. Thus, the conclusion regarding the comparison of recurrent prolapse rates is not valid.

The Withagen series

The Withagen group published 2 articles on the same study population, one with the primary 1-year outcomes of the RCT[667] and a secondary analysis of new prolapse in the untreated compartment.[668] In addition, a prospective cohort study reported predictors of failure after Prolift procedures.[669]

The study population was restricted to women with recurrent prolapse, although almost half (47%) had only stage II prolapse. Patients were randomly assigned to conventional prolapse repair (n=97) or Prolift procedures (n=93). Conventional prolapse repair included anterior and/or posterior colporrhaphy and sacrospinous or uterosacral ligament suspension. The Prolift procedures included anterior, posterior, or total procedures; 7 patients in the Prolift group also underwent conventional apical repair.

[667] Withagen MI et al. Trocar-guided mesh compared with conventional vaginal repair in recurrent prolapse. Obstet Gynecol 2011; 117: 242-250.
[668] Withagen MI, Milani AL, de Leeuw JW, Vierhout ME. BJOG. 2012 Feb;119(3):354-60. doi: 10.1111/j.1471-0528.2011.03231.x. Development of de novo prolapse in untreated vaginal compartments after prolapse repair with and without mesh: a secondary analysis of a randomised controlled trial.
[669] Milani AL, Withagen MI, Vierhout ME. Outcomes and predictors of failure of trocar-guided vaginal mesh surgery for pelvic organ prolapse. Am J Obstet Gynecol. 2012 Feb 1. [Epub ahead of print]

At 1 year, failure (defined as ≥ stage II prolapse) occurred in 38 of 84 (45%) of the non-mesh group and in 8 of 83 (9.6%) of the Prolift group. In the Discussion, the authors commented that "… asymptomatic patients with pelvic organ prolapse stage II could be forerunners and might develop complaints within a few years." This may be particularly true for patients in the Prolift group; for example, in the Hiltunen series of articles, the level of recurrent prolapse in the non-mesh group remained stable over time, while the level of recurrent prolapse in the mesh group nearly doubled from 1 year to 3 years of follow-up.[670]

In contrast to the anatomic outcomes, subjective improvement occurred in equal proportions in both groups, 64 of 80 (80%) in the non-mesh group and 63 of 78 (81%) in the Prolift group. Both groups experienced a similar decrease in symptoms and improvement of quality of life measured by the Urogenital Distress Inventory (UDI).

Intraoperative and postoperative complications were more frequent in the Prolift group versus the non-mesh group, including bladder injury in 2 versus 0 patients, hematoma in 6 versus 1 patients, and temporary urinary retention in 16 versus 5 patients. Levels of new-onset pain, dyspareunia, and stress incontinence were similar in both groups. In the Prolift group, 14 of 83 women (16.9%) developed mesh exposure, and 5 women required surgical treatment; 7 women had persistent mesh exposure at 1-year follow-up. Overall reoperation occurred at similar levels in the 2 groups, 5 patients in the Prolift group (mesh exposure) and 5 patients in the non-mesh group (1 for postoperative hemorrhage, 4 for recurrent prolapse).

In the Discussion, the authors expressed concern about the unknown effects of long-term presence of nonabsorbable mesh in the vagina and, because of this concern, suggested that Prolift be reserved for patients with recurrent prolapse.[671]

All authors disclosed financial conflicts of interest with Ethicon Women's Health and Urology, including unrestricted educational grant, consultancy agreements, and speaker's fees. The study was funded by university-administered research funds.

The second article[672] reported a much higher frequency of new prolapse in untreated compartments in the Prolift group. At 1 year after surgery, 10 of 59 women (17%) in the non-

[670] ETH-60188: Hiltunen R et al. Low-weight polypropylene mesh for anterior vaginal wall prolapse: a randomized controlled trial. Obstet Gynecol 2007; 110 (2 Pt 2): 455-462.
ETH-76654: Nieminen K et al. Symptom resolution and sexual function after anterior vaginal wall repair with or without polypropylene mesh. Int Urogynecol J 2008; 19: 1611-1616. Epub 21 Aug 2008.
PLTMEDLIT01406: Nieminen K et al. Outcomes after anterior vaginal wall repair with mesh: a randomized controlled trial with a 3 year follow-up. Am J Obstet Gynecol 2010 (3): 235.e1-8. Epub 2010 May 21.
[671] Withagen MI et al. Trocar-guided mesh compared with conventional vaginal repair in recurrent prolapse. Obstet Gynecol 2011; 117: 242-250. "The effects of long-term presence of nonabsorbable mesh in the vagina is unknown and a reason for concern. …" "Because the long-term effects and safety of mesh-reinforced repairs are not yet fully known, surgeons may consider these procedures primarily for recurrent vaginal prolapse after counseling patients on the risks and benefits. …"

mesh group versus 29 of 62 women (47%) in the Prolift group were diagnosed with new prolapse stage II or higher in the untreated compartment. In the Prolift group, women with new prolapse were significantly bothered as reflected in a higher score (13.1 ± 24.2) in the prolapse domain of the UDI, compared to women without new prolapse (2.9 ± 13.9). Of interest, when additional apical support was performed with anterior Prolift, the development of new prolapse was significantly reduced, underscoring the inadequacy of the anterior Prolift procedure to provide sufficient apical support.

The third article reported on 433 patients with 1-year follow-up after Prolift procedures.[673] Failure (defined as recurrent prolapse ≥ stage II) in the treated compartment occurred in 15%. Overall failure in any compartment occurred in 41%. Failure defined as prolapse beyond the hymen and the presence of vaginal bulge symptoms or repeat surgery occurred in 9%. A consistent predictor of failure for all definitions was the combined anterior/posterior Prolift procedure with uterine conservation.

In yet another article, Surgical Management of mesh-related complications after prior pelvic floor reconstructive surgery with mesh, Int. Urogyn. Journal (2011), 22:1395-1404, Withagen and her co-authors evaluated mesh complications and treatment, including with the Prolift. Among other things, the authors recognized that the majority of patients undergoing surgical care of mesh complications did not respond to conservative therapy and nearly one-third underwent prior mesh excision before coming to their facility for treatment. (1399). The authors discussed the most common and debilitating complications, including contraction, erosion/exposure, pain, and dyspareunia, and the need for extensive treatment to care for these complications. They also discussed mesh based complications occurring up to 18 years after mesh insertion, and the pervasive need for repeat excisions over time. Prolifts in particular demonstrated an 11% rate of patients requiring mesh excision. (1402). Finally, the authors recognized that "New meshes are introduced into clinical practice despite the lack of proper studies showing their safety and effectiveness," and that users shoud be "very experienced surgeons."

Maher et al[674]

This article reported 2-year outcomes after laparoscopic sacral colpopexy (n=53) versus total Prolift (n=55) for women with posthysterectomy vaginal vault prolapse. Two-thirds of the study population had previous surgery for prolapse or urinary incontinence. Although preoperative prolapse stage was not provided, entry criterion required that women had at least

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[672] Withagen MI, Milani AL, de Leeuw JW, Vierhout ME. BJOG. 2012 Feb;119(3):354-60. doi: 10.1111/j.1471-0528.2011.03231.x. Development of de novo prolapse in untreated vaginal compartments after prolapse repair with and without mesh: a secondary analysis of a randomised controlled trial.

[673] Milani AL, Withagen MI, Vierhout ME. Outcomes and predictors of failure of trocar-guided vaginal mesh surgery for pelvic organ prolapse. Am J Obstet Gynecol. 2012 Feb 1. [Epub ahead of print]

[674] Maher CF et al. Laparoscopic sacral colpopexy versus total vaginal mesh for vaginal vault prolapse: a randomized trial. Am J Obstet Gynecol 2011; 204: 360.e1-7.

stage II vaginal vault prolapse, and average baseline POPQ point C was 2.6-2.8 cm beyond the hymen, indicating advanced prolapse.

Objective success, defined as < stage II prolapse at all sites, was more frequent after laparoscopic sacral colpopexy, 41 of 53 (77%), than after Prolift, 23 of 55 (43%). Symptomatic prolapse occurred in 1 woman after laparoscopic sacral colpopexy and 4 women after Prolift. Although both groups experienced similar improvements in quality of life, satisfaction was higher in the laparoscopic sacral colpopexy group (87 ± 21) than in the Prolift group (79 ± 20). The authors attributed this difference in patient satisfaction to the much higher reoperation rate in the Prolift group. In the laparoscopic sacral colpopexy group, 3 women (5.7%) had surgery (1 each for TVT, trocar hernia, and mesh erosion), and in the Prolift group, 12 women (22%) had 15 reoperations (4 for mesh contracture, 3 for suburethral tapes, 3 for recurrent prolapse, and 2 for mesh erosion). Vaginal mesh erosion occurred in 1 patient in the laparoscopic sacral colpopexy group and 7 patients in the Prolift group.

Although the laparoscopic sacral colpopexy group had longer operating time compared with the Prolift group (median 97 minutes versus 50 minutes), intraoperative blood loss was less (median 100 mL versus 150 mL), hospital stay was shorter (median 2 days versus 3 days), and patients returned to normal activity an average of 5 days sooner.

The study was supported by competitive research grants from the Australian Gynaecological Endoscopy Society, 2007 and 2008; none of the authors reported financial or other conflicts of interests.

Post-Launch Articles Favorable to Mesh

2007, Abstract, Van Raalte et al[675]

This abstract was presented at the 2007 meetings of the Society of Gynecologic Surgeons and the International Urogynecological Association. This was a retrospective multicenter study of 350 patients after Prolift procedures between February 2005 and May 2006, with median follow-up of 6 months (range, 0.5-14 months). The authors reported recurrent prolapse in 33 patients (9.4%), with 11 (33.3%) requiring reoperation in this short period of follow-up. Reoperations for other indications were not reported. Intraoperative and early postoperative complications included cystotomy in 9 patients, ureteral obstruction in 1 patient, and hematoma in 1 patient. Postoperative complications included mesh exposure in 4 patients (1.1%), treated with office mesh excision and/or vaginal estrogen; new overactive bladder symptoms in 14 patients; new stress incontinence symptoms in 8 patients; voiding dysfunction in 12 patients; constipation in 31 patients; and dyspareunia in 22 patients. In the conclusion of the abstract, the authors cautioned that “Dyspareunia and vaginal pain are a concern for use in young, sexually active patients.”

[675] ETH-02668: Van Raalte H et al. Short-term results of the Prolift procedure in 350 patients used in the treatment of pelvic organ prolapse [abstract]. Int Urogynecol J 2007; 18 (Suppl 1): S49.

In the draft manuscript,[676] more than one-third of the patients had only stage I or II prolapse at baseline, and in only one-quarter of the cases was the total Prolift procedure performed. In the Discussion section, the authors describe in detail their concern that the risk of dyspareunia is increased in certain types of patients:

> … a more troubling concern of transvaginal mesh is de novo or worsened dyspareunia following its placement. … Of note, nearly all (5 of 6) patients with persistent post-operative dyspareunia carried pre-existing diagnosis of interstitial cystitis, chronic lower back pain and sciatica, fibromyalgia, or endometriosis…..Based on our outcomes, patients with chronic pain conditions, pre-existing pelvic pain and a history of pelvic surgery should be carefully counseled about the potential risk of post-operative dyspareunia and avoidance of mesh use should be considered…. Similarly, younger, sexually active patients should be counseled regarding the potential for dyspareunia following mesh placement and alternative treatment options should be discussed.

Since these physicians were among the most experienced Prolift users, the description of complications and contraindications should have been of great concern to Ethicon, yet the described need for warnings and patient selection criteria continued to be ignored by Ethicon.

2010, Murphy et al[677]

This is a retrospective study of 40 women who underwent vaginal hysterectomy concomitant with Prolift procedures. The authors described that Prolift mesh was not placed behind the vaginal cuff closure, and "T"-incisions were not used. With median follow-up of 12 months (range, 4-43 months), mesh exposure developed in 1 woman (2.5%). The authors concluded that "When incisions for mesh placement are kept separate from the vaginal cuff, transvaginal mesh reconstruction can be safely performed at the time of hysterectomy."

In the Discussion, the authors acknowledged the insidious risk of mesh erosion (not warned of by Ethicon):

> **It can certainly be agreed that the 20% of patients in this series that had less than 1 full year of follow-up precludes us from seeing some late erosions. In fact, even 2 or 3 years of follow-up without erosion does not guarantee a future free from erosion; there is no safe time for erosion when permanent materials are used.**

[676] ETH-02683: Van Raalte H et al. Short-term results of the Prolift procedure in 349 patients used in the treatment of pelvic organ prolapse [draft manuscript]. This article was never published.
[677] Murphy M et al. Vaginal hysterectomy at the time of transvaginal mesh placement. Female Pelvic Med Reconstr Surg 2010; 16: 272-277.

Murphy et al on behalf of the Pelvic Surgeons Network*[678]

*The signatories included Richard Bercik, M.D. (Pam Wicker) and Kevin Benson, M.D. (Linda Gross), both of whom signed the referenced letter, and both of whom have significantly narrowed their patient selection criteria for surgery with vaginal mesh of any nature. Moreover, both Dr. Bercik and Dr. Benson have abandoned use of the Prolift procedure due to concerns about safety with the Prolift procedure; as of his deposition Dr. Benson used only the Prolift + M procedure with a small number of patients and with a 4-hour informed consent process. Both testified that if they knew at the time they counseled these patients what they know now about the risks and complications of the Prolift procedure, the Prolift procedure would likely not have been used with either Mrs. Wicker or Mrs. Gross.

This article was written in response to the second FDA safety communication, UPDATE on Serious Complications Associated with Transvaginal Placement of Surgical Mesh for Pelvic Organ Prolapse. It is critically important to note that 5 of the 6 listed authors have strong financial conflicts of interests from receiving support from different mesh and prolapse kit manufacturers, including 4 of the 5 authors receiving payment for services from Ethicon.[679] As previously discussed, such strong financial conflicts of interest virtually always lead to substantial bias. Indeed, this article is written in such a way as to clearly reveal the authors' bias toward the products and procedures sold by the companies from whom the authors received payment.

Similar to the way Ethicon misused citations from the medical literature to support its claims, the authors of this article also selectively misused data from the literature in a skewed way to support their own claims. For example, when discussing the relative risk of complications from transvaginal mesh procedures versus native tissue repair (traditional vaginal prolapse surgery), the authors cited merely one article published in 2000 that reported an 11% risk of ureteral injury from uterosacral ligament suspension.[680] The authors ignored the findings of a systematic review and meta-analysis of uterosacral ligament suspension, which reported ureteral obstruction in only 1.8% of cases (15 of 820) and that required treatment other than intraoperative suture removal in only 0.6% of cases (5 of 820).[681]

The authors disagreed with the FDA's statement that transvaginal mesh surgery may expose patients to greater risk than traditional non-mesh repairs, claiming that this statement by the FDA was unsupported by evidence. The authors provided no citations to support their own claim and ignored evidence in the literature that confirmed the FDA's statement, including a

[678] Murphy M et al. Time to rethink: an evidence-based response from pelvic surgeons to the FDA Safety Communication: "Update on Serious Complications Associated with Transvaginal Placement of Surgical Mesh for Pelvic Organ Prolapse." Int Urogynecol J 2012; 23: 5-9.
[679] Miles Murphy, Heather van Raalte, Howard Goldman, and Vincent Lucente
[680] Barber MD et al. Bilateral uterosacral ligament vaginal vault suspension with site-specific endopelvic fascia defect repair for treatment of pelvic organ prolapse. Am J Obstet Gynecol 2000; 183: 1402–1411.
[681] PLTMEDLIT00012: Marguiles RU, Rogers MAM, Morgan DM. Outcomes of transvaginal uterosacral ligament suspension: systematic review and metaanalysis. Am J Obstet Gynecol 2010; 202: 124-134.

systematic review of apical vaginal prolapse repair that concluded that the "Rate of complications requiring reoperation and total reoperation rate was highest for vaginal mesh kits despite lower reoperation for prolapse recurrence and shorter overall follow-up" when compared with traditional vaginal prolapse surgery and sacrocolpopexy.[682] In addition, the authors claimed that "… while the rates of 'complication' may be higher with TVM, the severity of complications associated with ASC may be greater" and cited 1 article that described gastrointestinal morbidity after abdominal sacrocolpopexy.[683] Again, the authors ignored the findings of a systematic review that directly contradicted their claim that the severity of complications after transvaginal mesh may be lower than after abdominal sacrocolpopexy.[684] Based on 5639 patients from 52 studies with mean follow-up of 26.5 ± 20.1 months after sacrocolpopexy, the mean complication rate was 17.1%, with most complications requiring pharmacologic intervention (5.8%) or no intervention (5.5%), and the total reoperation rate was 7.1%. In contrast, based on 3425 patients from 24 studies with mean follow-up of 17.1 ± 13.8 months after vaginal mesh kits, the mean complication rate was 14.5%, with most complications requiring surgical intervention under general anesthesia (Dindo classification IIIb), and the total reoperation rate was 8.5%, despite having the shortest duration of follow-up. As discussed elsewhere in this report, since transvaginal mesh implantation confers a LIFE-LONG risk of mesh-related complications, the cumulative frequency of mesh-related complications will only increase as the duration of follow-up increases.

The authors disagreed with the FDA in its statement that "Mesh used in transvaginal POP repair introduces risks not present in traditional non-mesh surgery for POP repair." The authors claimed that "This statement implies that there are multiple risks of TVM [transvaginal mesh surgery] that do not exist with traditional repairs. This is not accurate and is misleading to the public." On the contrary, transvaginal mesh surgery does indeed introduce multiple unique risks, particularly when performed using trocar-based mesh kits, that are not present in traditional prolapse surgery. First, it is critically important to emphasize that the risks of mesh-related complications are LIFE-LONG, in stark contrast to risks associated with non-mesh prolapse surgery, which are restricted to the perioperative period. The only exception is the risk of recurrent prolapse, and this risk applies to transvaginal mesh surgery as well. Second, despite the authors' claim that mesh erosion is the only risk introduced by transvaginal mesh surgery, additional mesh-related complications include mesh contraction (associated with higher risks of vaginal mesh exposure, vaginal pain, dyspareunia, and recurrent prolapse); vaginal stiffness and loss of pliability and expansibility due to fibrosis around the mesh implant; and mesh erosion and/or fistula formation into adjacent organs, including the bladder, rectum, and urethra. Furthermore, the trocar-based transvaginal mesh kits introduce novel and severe risks of intraoperative injury that do not exist with non-mesh, non-trocar-based prolapse surgery. The blind passage of multiple trocars through complex pelvic anatomy introduces risks of organ

[682] Diwadkar GB, Barber MD, Feiner B, Maher C, Jelovsek JE. Complication and reoperation rates after apical vaginal prolapse surgical repair: a systematic review. Obstet Gynecol 2009 Feb; 113: 367-373.
[683] Whitehead WE et al. Gastrointestinal complications following abdominal sacrocolpopexy for advanced pelvic organ prolapse. Am J Obstet Gynecol 2007; 197: 78.e1–78.e7.
[684] Diwadkar GB, Barber MD, Feiner B, Maher C, Jelovsek JE. Complication and reoperation rates after apical vaginal prolapse surgical repair: a systematic review. Obstet Gynecol 2009 Feb; 113: 367-373.

injury (bladder, rectum, and urethra), nerve injury, and blood vessel injury resulting in excessive intraoperative and/or postoperative blood loss, hematoma formation, need for transfusion, need for operative drainage, and abscess formation. The authors did not address or even mention any of these risks, nor did they provide any evidence of their own to support their disagreement with the FDA's statement. As mentioned above, a systematic review found the highest rate of complications from vaginal mesh kits, including the highest total reoperation rate.[685] This was despite the shortest duration of follow-up in studies of vaginal mesh kits; because the risk of mesh-related complications is life-long, the rate of complications from vaginal mesh kits will only increase with time.

In attempting to explain the reported variation in mesh exposure frequency, the authors stated that "Since the same mesh and delivery system were used in similar patient populations, it is reasonable to conclude that this variation is not a function of the mesh itself but rather the surgical technique." Far from supporting their position, however, this statement emphasized what Ethicon knew all along, that surgical technique, as practiced by surgeons with differing skill levels and, by definition, inexperienced with the Prolift procedure, would have an important impact on patient outcomes. As noted previously, large variations in outcomes were found as early as the first TVM studies and could only be expected to increase as the Prolift procedure became more widely used in the surgical community.

With regard to vaginal mesh exposure, based on only 1 citation, the authors claimed that "More than half of most mesh exposures from TVM are asymptomatic, and one third need only minor outpatient operative intervention."[686] Again, rather than provide a fair and balanced review of the available medical literature or cite from one of several systematic reviews now available, the authors selected only 1 citation in an attempt to minimize the patients' experience of mesh exposure and the need for treatment, particularly surgical treatment. One systematic review reported mesh exposure in 10.3% based on 10,440 patients in 91 studies, and management was reported in 795 women in 76 studies (unfortunately, the proportion of symptomatic patients was not reported).[687] Treatment was required in almost all women, including nonsurgical treatment in 21%, in-office mesh excision in 11%, and surgical excision in the operating room in 56%; the article also stated that some women required multiple additional procedures, although numerical data were not provided. Therefore, in contrast to the biased and selective reporting from Murphy et al that only one-third of women need minor outpatient operative intervention, this systematic review reported the need for surgery to treat mesh exposure in two-thirds of women (67%), the majority of them requiring mesh excision in the operating room. Even this systematic review underestimated the true frequency of vaginal mesh exposure, because follow-up in the included studies only extended to 12 months. As noted

[685] Diwadkar GB, Barber MD, Feiner B, Maher C, Jelovsek JE. Complication and reoperation rates after apical vaginal prolapse surgical repair: a systematic review. Obstet Gynecol 2009 Feb; 113: 367-373.
[686] Withagen MI et al. Trocar-guided mesh compared with conventional vaginal repair in recurrent prolapse: a randomized controlled trial. Obstet Gynecol 2011; 117: 242–250.
[687] Abed H et al. Incidence and management of graft erosion, wound granulation, and dyspareunia following vaginal prolapse repair with graft materials: a systematic review. Int Urogynecol J 2011; 22: 789-798. Epub March 22, 2011.

previously, since the risk of mesh-related complications is LIFE-LONG, the frequency of mesh exposure and the need for treatment will only increase with time.

The authors provided misleading data in an attempt to show that mesh exposure occurs at similar frequencies after sacrocolpopexy and transvaginal mesh surgery, by stating that "… in two large, multicenter trials conducted by surgeons who perform the index surgery on a regular basis, the results of the abdominal and vaginal approach are quite similar. In the TVM trial that randomized over 400 subjects, 3.2% had undergone a procedure to correct mesh erosion at 12 months. In a well-known RCT of 322 women undergoing ASC, the erosion rate at 12 months was 4.3% …" However, in the first trial cited,[688] 3.2% represents the proportion of women requiring surgical treatment for mesh exposure, while in the second trial, 4.3% represents only the frequency of mesh or suture exposure, not those requiring surgical treatment.[689]

The authors claim that the FDA arbitrarily singled out transvaginal mesh procedures for critique by stating that "… we are simply suggesting that this singling out of TVM by the FDA seems arbitrary based on a lack of reporting systems for the other procedures." This is disingenuous and again reveals the authors' bias in defending Ethicon's unethical and misleading business practices in promoting the Prolift procedure as if it were safe and effective. The "other procedures" that the authors refer to are not commercial products, and they were not aggressively marketed to fill a so-called need in vaginal prolapse surgery as was the Prolift procedure. As the manufacturer of the Prolift procedure, it was (and is) Ethicon's obligation to ensure its safety and appropriately warn physicians and patients of critically important risks of the Prolift procedure before advocating its widespread use. In addition, it was (and is) Ethicon's obligation to demonstrate conclusively that additional risks incurred due to the Prolift procedure were outweighed by substantial benefits. Ethicon failed to meet either of these obligations.

The FDA stated that "There is no evidence that transvaginal repair to support the top of the vagina (apical repair) or the back wall of the vagina (posterior repair) with mesh provides any added benefit compared to traditional surgery without mesh." The authors agreed with the FDA's statement, but they claimed that "this issue is more complex than this statement implies." In discussing trials that assessed apical repairs, they went on to claim that "… of the 287 subjects in these three trials, only six (2%) had apical failures. Therefore, apical failure (as defined in most RCTs) is not a very useful parameter to distinguish the anatomic success between POP procedures." The contorted logic behind this conclusion again reveals the authors' bias in attempting to defend transvaginal mesh procedures despite the obvious implications of available evidence. Based on the very low rate of apical failure in these trials, a less biased conclusion would be that since apical failure occurs so uncommonly with non-mesh prolapse surgery, it would be very difficult to demonstrate a benefit for using vaginal mesh to treat apical prolapse.

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[688] Altman D et al. Anterior colporrhaphy versus transvaginal mesh for pelvic-organ prolapse. N Engl J Med 2011; 364: 1826–1836.

[689] Brubaker L et al. Two-year outcomes after sacrocolpopexy with and without Burch to prevent stress urinary incontinence. Obstet Gynecol 2008; 112: 49–55.

Regarding the use of mesh for posterior vaginal prolapse, the authors stated that "Contrary to the FDA's above statement, one of these three (a study of recurrent prolapse repair) did show superiority of mesh over nonmesh repairs in the posterior wall at 1 year of follow-up (4.1% failure in the mesh vs 24.5% in the nonmesh group, P = 0.003)."[690] Again, the authors selected only 1 study in an attempt to support their claim, while the FDA formed their conclusion based on evaluating the available evidence as a whole. In addition, the Withagen study cited found no difference in subjective outcomes between mesh and nonmesh repairs.

The authors acknowledged the paucity of data studying the effect of transvaginal mesh surgery for posterior vaginal prolapse. Several factors may contribute to this, including the satisfactory outcomes after traditional posterior vaginal prolapse repair and the reluctance of surgeons to use permanent mesh in posterior vaginal prolapse repair, due to fears of incurring mesh-related complications out of proportion to any expected benefit. Experts believe that traditional posterior vaginal prolapse repair provides adequate outcomes with minimal complications.[691] In addition, experts are concerned about mesh-related complications, particularly when mesh is placed in the posterior vagina and when used in sexually active women, for fear of creating dyspareunia and pain that is difficult if not impossible to effectively treat.[692]

The authors took issue with the FDA's statement that "While transvaginal surgical repair to correct weakened tissue between the bladder and vagina (anterior repair) with mesh augmentation may provide an anatomic benefit compared to traditional POP repair without mesh, this anatomic benefit may not result in better symptomatic results." Instead, the authors claimed that "Given the current data, it would be equally true to state that 'this anatomical benefit may result in better symptomatic results'." However, this claim ignored the data as they actually exist, not as they may exist. Of the 7 randomized trials that compared both anatomic and symptomatic outcomes with transvaginal mesh surgery versus traditional non-mesh vaginal

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[690] Withagen MI et al. Trocar-guided mesh compared with conventional vaginal repair in recurrent prolapse: a randomized controlled trial. Obstet Gynecol 2011; 117: 242–250.

[691] Roundtable: Using mesh to repair prolapse calls for more than a kit – it takes skill. Karram MM, moderator. OBG Management 2009; 21 (1): 25-36. Dr. Walters: "For posterior vaginal wall prolapse and rectocele, I firmly believe, based on our research and that of others, that sutured repairs are superior to graft-augmented surgery." Citation to Paraiso MF et al. Rectocele repair: a randomized trial of three surgical techniques including graft augmentation. Am J Obstet Gynecol 2006; 195: 1762-1771.
Dr. Karram: "I haven't found a definite indication for mesh augmentation. We have used biologic meshes empirically, but I am not convinced that they really add long-term durability, regardless of whether they are used in the anterior or posterior vaginal segment. Our published durability rate for traditional suture-type repairs is in the range of 85% at 5 years out." Citation to Silva WA et al. Uterosacral ligament vault suspension: five-year outcomes. Obstet Gynecol 2006; 108: 255-263.

[692] Roundtable: Using mesh to repair prolapse calls for more than a kit – it takes skill. Karram MM, moderator. OBG Management 2009; 21 (1): 25-36. Dr. Karram: "Even if I assumed that mesh would give me 100% 5-year durability, this rate would have to be at the expense of some erosion, pain, and other complications unique to mesh. I do not think that the potential improvement in durability is worth these potential complications."
ETH-59479, Prolift physician IDI, May 16-21, 2008: Disadvantages of Prolift: not appropriate for posterior repair (either not needed or high risk of dyspareunia); Concern about use in young, sexually active patients with potential for postoperative dyspareunia.

prolapse surgery, only 1 showed better results in symptomatic outcomes for transvaginal mesh surgery,[693] while the remaining 6 trials showed no difference in symptomatic outcomes between transvaginal mesh surgery and traditional non-mesh vaginal prolapse surgery.[694] Therefore, when evaluating ALL available data in a fair and unbiased way, the preponderance of data showed that "better" anatomic outcomes do NOT translate into better symptomatic outcomes. Indeed, in one article reporting sexual dysfunction after transvaginal mesh surgery, the authors commented that vaginal anatomy at stage 0 may represent an overcorrection, leading to more rather than fewer symptoms.[695] This overcorrection may, in part, explain findings that prolapse in the non-mesh-treated compartment was much more frequent after transvaginal mesh surgery than after traditional non-mesh vaginal prolapse surgery.[696]

In yet another example of selective reporting while ignoring the preponderance of data, the authors claimed that "While [mesh] contraction may occur in some cases, analysis of translabial four-dimensional ultrasounds of 40 patients who underwent anterior mesh procedures showed no evidence of mesh contraction between their first and last postoperative visits. This is only one imaging study, and the results have not yet been duplicated …" The authors implied that the article cited[697] was the only study using ultrasound to assess mesh contraction after transvaginal mesh surgery; this is not the case and, in fact, 3 other articles published before the cited 2011 article found evidence of substantial mesh contraction after transvaginal mesh

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[693] Altman D et al. Anterior colporrhaphy versus transvaginal mesh for pelvic-organ prolapse. N Engl J Med 2011; 364: 1826–1836.

[694] Sivaslioglu AA et al. A randomized comparison of polypropylene mesh surgery with site-specific surgery in the treatment of cystocele. Int Urogynecol J 2008; 19:467-471. Epub September 28, 2007.

ETH-60188: Hiltunen R et al. Low-weight polypropylene mesh for anterior vaginal wall prolapse: a randomized controlled trial. Obstet Gynecol 2007; 110 (2 Pt 2): 455-462.

ETH-76654: Nieminen K et al. Symptom resolution and sexual function after anterior vaginal wall repair with or without polypropylene mesh. Int Urogynecol J 2008; 19: 1611-1616. Epub 21 Aug 2008.

PLTMEDLIT01406: Nieminen K et al. Outcomes after anterior vaginal wall repair with mesh: a randomized controlled trial with a 3 year follow-up. Am J Obstet Gynecol 2010 (3): 235.e1-8. Epub 2010 May 21.

ETH-76667: Nguyen JN, Burchette RJ. Outcome after anterior vaginal prolapse repair: a randomized controlled trial. Obstet Gynecol 2008; 111: 891-898.

ETH-76774: Carey M et al. Vaginal repair with mesh versus colporrhaphy for prolapse: a randomized controlled trial. BJOG 2009; 116: 1380-1386. Epub 7 July 2009.

Iglesia CB, Sokol AI, Sokol ER, Kudish BI, Gutman RE, Peterson JL, Shott S. Vaginal mesh for prolapse: a randomized controlled trial. Obstet Gynecol 2010; 116: 293-303.

Sokol AI et al. One-year objective and functional outcomes of a randomized clinical trial of vaginal mesh for prolapse. Am J Obstet Gynecol 2012; 206: 86.e1-9.

Withagen MI et al. Trocar-guided mesh compared with conventional vaginal repair in recurrent prolapse. Obstet Gynecol 2011; 117: 242-250.

[695] PLTMEDLIT-00564: Altman D, Elmer C, Kiiholma P, et al. Sexual dysfunction after trocar-guided transvaginal mesh repair of pelvic organ prolapse. Obstet Gynecol 2009; 113: 127-133. "In a predominantly parous and postmenopausal population, stage 0 may be considered a surgical overcorrection of vaginal anatomy. Anatomical overcorrection and tautness of the mesh may compromise vaginal elasticity, give rise to vaginal tension, and prevent swelling of the vagina at sexual arousal."

[696] Withagen MI, Milani AL, de Leeuw JW, Vierhout ME. BJOG. 2012 Feb;119(3):354-60. doi: 10.1111/j.1471-0528.2011.03231.x. Development of de novo prolapse in untreated vaginal compartments after prolapse repair with and without mesh: a secondary analysis of a randomised controlled trial.

[697] Dietz HP et al. Mesh contraction: myth or reality? Am J Obstet Gynecol 2011; 204 (173): e1–e4.

surgery.[698] Even the cited article that claimed mesh contraction did not occur did indeed find evidence of mesh contraction of 35%.[699]

The first FDA recommendation stated that "Recognize that in most cases, POP can be treated successfully without mesh thus avoiding the risk of mesh-related complications." The authors claimed that this recommendation was misleading and that "The validity of this recommendation depends on how 'most cases' is being defined. Studies show that traditional POP repairs can have high rates of failure." The authors cited the Olsen et al and Clark et al studies to support this claim that traditional prolapse repairs have high rates of failure.[700] As noted previously, Ethicon has also cited these same articles in an attempt to justify the need for mesh use in prolapse repair while ignoring more current literature.

The authors attempted to portray the long-term safety of transvaginal mesh surgery in the absence of evidence by stating that "Finally, there are long-term data on the transvaginal placement of mesh for urinary incontinence that does not show any untoward effects of mesh long term that were not present in the short term." The authors completely ignored one of the most important predictors of complications with mesh implantation, which is the amount (surface area) of mesh implanted. As discussed in other parts of this report, the greatly increased mesh burden from mesh implantation in transvaginal mesh surgery is directly related to increased chronic inflammatory and foreign body response, which leads to many of the most common mesh-related complications, including mesh exposure and mesh contraction. The authors ignored all the evidence in that regard and provided no citations to support their contention that mesh implantation in urinary incontinence surgery produces similar or equivalent effects as mesh implantation in transvaginal prolapse surgery.

Finally, the authors made a claim about patient selection for transvaginal mesh surgery by stating that "No one is suggesting that mesh is recommended for all patients." Yet this is exactly what Ethicon did, as discussed in detail in other parts of this report. As just two examples demonstrate, Ethicon marketed the Prolift procedure directly to patients with pelvic pain and patients who smoke, groups who were later identified at being at such high risk for severe and sometimes permanent complications after the Prolift procedure that the Prolift procedure is now considered to be contraindicated for these patients.

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[698] PLTMEDLIT-01252 (cited in ETH-02326): Tunn R, Picot A, Marschke J, Gauruder-Burmester A. Sonomorphological evaluation of polypropylene mesh implants after vaginal mesh repair in women with cystocele or rectocele. Ultrasound Obstet Gynecol 2007; 29: 449-452. Epub 1 March 2007.
PLTMEDLIT-01247 (cited in ETH-02314): Shek KL, Dietz HP, Rane A, Balakrishnan S. Transobturator mesh for cystocele repair: a short- to medium-term follow-up using 3D/4D ultrasound. Ultrasound Obstet Gynecol 2008; 32: 82-86. Epub 10 June 2008.
Velemir L et al. Transvaginal mesh repair of anterior and posterior vaginal wall prolapse: a clinical and ultrasonographical study. Ultrasound Obstet Gynecol 2010; 35: 474-480.
[699] Dietz HP et al. Mesh contraction: myth or reality? Am J Obstet Gynecol 2011; 204 (173): e1–e4.
[700] Olsen AL et al. Epidemiology of surgically managed pelvic organ prolapse and urinary incontinence. Obstet Gynecol April 1997; 89:501-506.
Clark AL et al. Epidemiologic evaluation of reoperation for surgically treated pelvic organ prolapse and urinary incontinence. Am J Obstet Gynecol 2003; 189: 1261-1267.

Lucente IIS Database

The literature authored by Dr. Lucente, Dr. Murphy, and their group, was, as set forth above, a centerpiece of the information used by Ethicon to try to demonstrate the safety and efficacy of the Prolift, cited in professional education, marketing and sales documents, the Prolift Monograph, and others. Vincent Lucente was paid substantial sums to speak about the benefits and safety of the Prolift on behalf of Ethicon. In a 2010 email, Piet Hinoul unequivocally stated that "nobody believes" the extremely low erosion rates published by that group, and confirmed this view in his deposition. I was provided and had the opportunity to review the internal data of Lucente and Murphy, known as the Lucente/Murphy Prolift IIS Database, related documents and studies, and the depositions of Dr. Lucente and Dr. Murphy with the exhibits addressed in those depositions.

Even with limitations due to high loss to follow-up and the short duration of follow-up of at most 1 year, the data in the Prolift IIS spreadsheet demonstrates unequivocally that the Prolift procedure is neither safe nor effective, with an unacceptable risk benefit profile, and further confirms that Ethicon-sponsored studies, and studies performed by Ethicon's paid consultants, are largely unreliable and fail to accurately reflect the unfavorable risk/benefit profile for the Prolift. Complications occurred in the vast majority of patients (85%). Of greatest concern was the frequency of serious complications, including the need for reoperation in 29% of the patients and mesh complications in 28%. Even this high rate of mesh complications was an underestimate because mesh contraction was not recorded. Worse yet, this lack of safety was accompanied by an extremely high rate of recurrent prolapse, 49.7%, and clinical failure requiring retreatment for recurrent prolapse of 12.7%. This was particularly worrisome given the very short duration of follow-up, at most 1 year, in these patients who are burdened with the risk of mesh complications and recurrent prolapse for the rest of their lives.

Introduction
The Prolift IIS database, an undated Excel spreadsheet, contained data on 514 patients with up to 1 year of follow-up. The Prolift surgical procedures were performed from August 29, 2005 to July 8, 2008.

1. Clinical Study Agreement, October 30, 2007, Protocol #300-08-002, "A Large Multicenter Database of Women Who Have Had and Are Going to have Surgical Correction of Their Pelvic Organ Prolapse using the Gynecare Prolift System"
   - Dr. Lucente was the principal investigator.
   - Under the terms of the Ethicon clinical study agreement, Dr. Lucente was contractually obligated to provide Ethicon with a final study report and to publish the study's findings in the peer-reviewed literature. Dr. Lucente fulfilled neither of these obligations; in fact, Dr. Lucente testified that he never analyzed, presented, or published outcomes for the 514 patients in the database.
   - In deposition testimony, Drs. Lucente and Murphy were unable to consistently identify the source of data for abstracts reporting on 451, 654, and 1172 patients in

whom they had performed Prolift procedures, including how many of these patients were represented in the Prolift IIS database. In the abstract purporting to report on 451 patients as a subset of patients in the Prolift IIS database, the outcomes were markedly inconsistent with the findings of my analysis.

- Despite the fact that as sponsor, Ethicon had ownership of the Prolift IIS data, Ethicon never requested or obtained the Prolift IIS database from Dr. Lucente and, obviously, Ethicon itself never analyzed the data in the Prolift IIS database. This failure on Ethicon's part is in direct contradiction to Johnson & Johnson publication policy and the testimony of Dr. James Hart, Chief Medical Officer and Vice President of Medical Affairs for Johnson & Johnson Global Surgery Group, in which he stated that results of an Ethicon-funded study should be published regardless of whether the results were favorable or unfavorable.
- If Ethicon had promptly and accurately analyzed these data that they owned, from their key preceptor and a very experienced Prolift surgeon from whom better than average results could be expected, they would have had to conclude that the Prolift procedure was neither safe nor effective, and its marketing should be suspended immediately and, if imprudently kept on the market, the warnings would have to be significantly enhanced, and the marketing significantly changed – for example, to stop promising superior anatomic prolapse recurrence rates compared to suture repairs.

2. Loss to follow-up
   - Loss to follow-up was extremely high, raising grave concerns regarding selection bias and the likelihood that women lost to follow-up suffered even worse outcomes than those women who maintained follow-up.
   - Only 26.7% of women attended 1-year follow-up.
   - Only 74.3% of women attended 4-month follow-up. Virtually all of the women who did not attend the 4-month visit were lost to follow-up completely.

3. Prolapse recurrence
   - Anatomic prolapse recurrence occurred in 49.7% of women.
   - Clinical Prolift failure requiring retreatment occurred in 12.7% of women. This is a high rate of failure, especially given the extremely short-term follow-up, giving the lie to Ethicon's data-free claims that the Prolift procedure "offers promising long-term results." By way of contrast, a systematic review reported reoperation for prolapse recurrence after traditional vaginal repair of only 3.9% with almost 3 years of follow-up (Diwadkar et al. Obstet Gynecol 2009; 113: 367-373).

4. Complications occurred in 85% of women overall.

5. Mesh complications occurred in 28% of women. Even this high frequency of mesh complications is an underestimate because mesh contraction was not assessed.

- Vaginal mesh erosion of 10.6% is also most likely an underestimate, as no new mesh erosions were recorded between 4 months and 1 year and also due to attrition.
- Granulation tissue occurred in 9.2% of women.
- "Problematic" vaginal incisions occurred in 7.0% of women.
- Mesh revision (for indications other than mesh erosion) occurred in 1.4% of women.

6. At the time most of the women in the Prolift IIS database were treated with the Prolift procedure, a protocol for data collection was not even in place, resulting in the haphazard retrospective collection of data with major systematic errors and incompleteness.
   - Basic demographic data such as age were not collected in the Prolift IIS database.
   - Various incomparable methods of assessing anatomic outcomes were used. In fact, some women were deemed a success even without recorded follow-up POPQ measurements.
   - Questionnaire data were frequently missing both at baseline and at follow-up. Even more important, it appears that the Pelvic Floor Distress Inventory (PFDI) questionnaire was administered incorrectly, thereby invalidating the responses to this key symptom and quality of life instrument. Based on those marked shortcomings of questionnaire administration and completion, I do not consider any of the questionnaire data to be reliable or even analyzable in a meaningful way.

7. Presentation of Prolift IIS data

   Dr. Murphy testified that any presentation of Prolift data that included the range of time of the IIS database was drawn from the same patient population. Dr. Murphy authored an article of clinical and research guidelines for vaginal graft use in which he stated that "Studies should state clearly whether the participants have been previously reported in published articles." However, Dr. Murphy and his co-authors failed to follow this basic principle of clinical research in reporting outcomes from the Prolift IIS database, with the end result that data in 6 abstracts and 3 articles likely represent some undefined portion of the same patient population. This practice has the effect of weighting the medical literature with a markedly skewed view of Prolift outcomes, particularly since complications were underreported and success overreported. Another example of the failure of Dr. Murphy and Dr. Lucente to follow the guidelines discussed in this article is the failure to adhere to the principle that "anatomic outcomes should be reported using the POP-Q system by an investigator not involved in and, when possible, blinded to the surgery." In fact, they performed their own POP-Q examinations, and Dr. Murphy testified that Dr. Lucente had a practice of not documenting POP-Q measurements, purportedly when the patient did not have recurrent prolapse. Such a practice has no support in any notion of Good Clinical Practice, likely is symptomatic of further invalid research practices, and demonstrates reliability issues for all of Dr. Lucente's studies.

   Dr. Lucente testified that the entirety of data in the Prolift IIS database was never analyzed, presented, or published. Instead, varying subsets of patients were selected and their outcomes reported without disclosing the full set of patients from which they were

drawn, or the lack of any consistently followed protocol at the time of treatment. In this way, the preferred results could be literally hand-picked from the data, which would in no way fairly and accurately represent the experience of the entire set of patients. Ethicon was apparently aware that the data reported by Dr. Lucente and Dr. Murphy was not reliable. For example, in one subset of 151 patients, the authors claimed that no patients had mesh erosion, prompting Dr. Hinoul to say "Who believes Mr Lucente's group when van Raalte publishes that they have NO erosions? Nobody!"

Another effect of selecting subsets from the entire dataset is that loss to follow-up was never accurately disclosed. As is well described in the literature, patients with complications are likely to discontinue care with the implanting surgeons and instead seek care elsewhere. This magnifies the effect of underreporting complications and overreporting positive outcomes. In one example, a 2009 abstract reported questionnaire data on 99 patients who had Prolift surgery in 2006-2007. Over the same period, the IIS database contained data on 365 patients. With median follow-up of only 4 months, the authors claimed that no patient experienced any complication, and they concluded that "quality of life and sexual function are significantly improved overall in patients" after the Prolift procedure.

In another example of overreporting positive outcomes, a 2009 abstract purported to describe 4-month and 1-year results after the Prolift procedure, with 451 patients overall and 181 patients with at least 1-year follow-up. (The 451 patients apparently represent some undefined portion of the 514 patients in the IIS database.) However, proportions of "success" and "failure" were based on the denominator of 451 patients, thus markedly elevating the supposed "cure rate." The "overall cure rate" was reported as 86.7%, based on 60 patients with recurrent prolapse, reported as 13.3% (60 of 451 patients). However, at any time a patient "fails," she cannot "un-fail" and must be counted accordingly. Therefore, the correct proportion of patients with recurrent prolapse should have been calculated as 60 of 181 patients, or 33%. Even these authors could not then have concluded that the Prolift procedure results in "high surgical cure rates."

The authors failed to consistently and accurately report Ethicon's funding of the Prolift IIS database. For example, in the 2009 abstract of 451 patients discussed in the preceding paragraph, the level of support was described as "Investigator initiated, no external funding," and the question as to whether the work was supported by industry was answered "No." Obviously, inaccuracies such as this defeat the purpose of financial disclosures and mislead the scientific community as to the purported absence of the well-known effect of industry sponsorship on reporting results.

In conclusion, these data and the testimony of Dr. Lucente and Dr. Murphy further establish the unacceptable risk/benefit profile of the Prolift.

Details of Prolift IIS Database Analysis

I. Database Patients' Characteristics

A. Dates of Prolift surgery
1. 2005 = 3 patients (0.6%)
2. 2006 = 96 patients (18.7%)
3. 2007 = 269 patients (52.3%)
4. 2008 to July 8 = 146 patients (28.4%)

B. Baseline stage (N=511, 3 patients [#79, 101, 236] missing baseline POPQ)
1. Stage 0: 9 patients (1.8%)
2. Stage 1: 18 patients (3.5%)
3. Stage 2: 232 patients (45.4%)
4. Stage 3: 235 patients (46.0%)
5. Stage 4: 17 patients (3.3%)

C. Prolift Procedures (N=514)
Overall
1. Anterior: 275 (53.5%)
2. Posterior: 80 (15.6%)
3. Total: 159 (30.9%)

By baseline stage of prolapse in Prolift-treated compartment(s):
1. Stage 0 = 9 patients
   a. 7 anterior Prolift = 78%
   b. 2 posterior Prolift = 22%
2. Stage 1 = 18 patients
   a. 11 anterior Prolift = 61%
   b. 7 posterior Prolift = 39%
3. Stage 2 = 232 patients
   a. 151 anterior Prolift = 65%
   b. 38 posterior Prolift = 16%
   c. 43 total Prolift = 19%
4. Stage 3 = 235 patients
   a. 97 anterior Prolift = 41%
   b. 31 posterior Prolift = 13%
   c. 107 total Prolift = 46%
5. Stage 4 = 17 patients
   a. 7 anterior Prolift = 41%
   b. 1 posterior Prolift = 6%
   c. 9 total Prolift = 53%
6. 3 patients without baseline POPQ: 2 anterior and 1 posterior Prolift

D. Concomitant surgery (N=514)
– 84% had concomitant slings (TVT type)

II. Loss to follow-up or missing data at or before 1 year

Loss to follow-up was extremely high, raising grave concerns regarding selection bias and the likelihood that women lost to follow-up suffered even worse outcomes than those women who maintained follow-up.

A. 1y visit: 377 of 514 = 73.3%
B. 4m visit: 132 of 514 = 25.7%
   Note that of the 132 patients who did not attend the 4m visit, only 5 patients attended the 1y visit.
C. 6w visit: 34 of 514 = 6.6%
D. 2w visit: 9 of 514 = 1.8%

III. Prolapse recurrence

Note that prolapse recurrence was not defined in the Prolift IIS proposal.

- In my analysis of the data, anatomic recurrence was defined as categorization as failure, support defect and/or recurrence in the database; any POPQ point > stage 1 at any postoperative time point; reoperation or retreatment for prolapse, regardless of which compartment was Prolift-treated; and/or worsening or same measures of prolapse compared to baseline in Prolift-treated compartment(s).
- Clinical failure was defined as prolapse that was treated with repeat surgery or pessary.
- Two calculations of anatomic recurrence and clinical failure were performed.
  1. At or before 1 year: this includes all patients with POPQ completed at 1-year follow-up plus patients with recurrence before 1 year without 1-year follow-up; patients without recurrence before 1 year without 1-year follow-up were considered lost to follow-up.
  2. At 1 year: this includes patients with recurrence at or before 1 year in only those patients with POPQ completed at 1-year follow-up.

A. Overall recurrence

   AT or BEFORE 1 YEAR

   1. Anatomic recurrence: 90 of 181 patients = 49.7%
      By recurrence in Prolift-treated or non-Prolift treated compartment(s)
      a. Prolift-treated compartment(s): 53 of 90 patients = 59%
      b. Non-Prolift-treated compartment(s): 31 of 90 patients = 34%
      c. Both Prolift-treated and non-Prolift-treated compartments: 5 of 90 patients = 6%
      d. Unknown type of anatomic recurrence: 1 of 90 patients = 1%

2. Clinical failure: 23 of 181 patients = 12.7%[701]
   By recurrence in Prolift-treated or non-Prolift treated compartment(s)
   a. Prolift-treated compartment(s): 14 of 23 patients (61%)
   b. Non-Prolift-treated compartment(s): 7 of 23 patients (30%)
   c. Both Prolift-treated and non-Prolift treated compartments: 1 of 23 patients (4%)
   d. Unknown type of clinical failure: 1 of 23 patients (4%)

AT 1 YEAR

1. Anatomic recurrence: 46 of 137 patients = 33.6%
   By recurrence in Prolift-treated or non-Prolift treated compartment(s)
   a. Prolift-treated compartment(s): 26 of 46 patients (57%)
   b. Non-Prolift-treated compartment(s): 15 of 46 patients (33%)
   c. Both Prolift-treated and non-Prolift treated compartments: 4 of 46 patients (9%)
   d. Unknown type of anatomic recurrence: 1 patient of 46 patients (2%)

2. Clinical failure: 16 of 137 patients = 11.7%
   By recurrence in Prolift-treated or non-Prolift treated compartment(s)
   a. Prolift-treated compartment(s): 10 of 16 patients (62.5%)
   b. Non-Prolift-treated compartment(s): 4 of 16 patients (25%)
   c. Both Prolift-treated and non-Prolift treated compartments: 1 of 16 patients (6%)
   d. Unknown type of clinical failure: 1 patient of 16 patients (6%)

B. Anatomic recurrence by baseline stage in Prolift-treated compartment(s)
   AT or BEFORE 1 YEAR

1. Stages 0-1: 6 of 9 patients = 67%
   a. 27 patients in total
   b. 18 patients LTF
   c. 3 patients without recurrence
   d. 6 patients with recurrence
   By recurrence in Prolift-treated or non-Prolift treated compartment(s)
      1) Prolift-treated compartment(s): 4 of 6 patients (67%)
      2) Non-Prolift-treated compartment(s): 2 of 6 patients (33%)

2. Stage 2: 32 of 72 patients = 44%
   a. 232 patients in total
   b. 160 patients LTF

[701] Contrast this with 8.6% (32 of 374 patients; 16 with surgery, 16 with pessary) with retreatment for prolapse after 2 years follow-up. Barber MD et al. Comparison of 2 transvaginal surgical approaches and perioperative behavioral therapy for apical vaginal prolapse: The OPTIMAL randomized trial. JAMA 2014; 311(10):1023-1034.

c. 40 patients without recurrence
d. 32 patients with recurrence

By recurrence in Prolift-treated or non-Prolift treated compartment(s)

1) Prolift-treated compartment(s): 13 of 32 patients = 41%
2) Non-Prolift-treated compartment(s): 16 of 32 patients = 50%
3) Both Prolift-treated and non-Prolift treated compartments: 3 of 32 patients = 9%

3. Stage 3: 48 of 93 patients = 52%
   a. 235 patients in total
   b. 142 patients LTF
   c. 45 patients without recurrence
   d. 48 patients with recurrence

   By recurrence in Prolift-treated or non-Prolift treated compartment(s)

   1) Prolift-treated compartment(s): 35 of 48 patients = 73%
   2) Non-Prolift-treated compartment(s): 11 of 48 patients = 23%
   3) Both Prolift-treated and non-Prolift treated compartments: 1 of 48 patients = 2%
   4) Unknown type of anatomic recurrence: 1 of 48 patients = 2%

4. Stage 4: 4 of 6 patients = 67%
   a. 17 patients in total
   b. 11 patients LTF
   c. 2 patients without recurrence
   d. 4 patients with recurrence

   By recurrence in Prolift-treated or non-Prolift treated compartment(s)

   1) Prolift-treated compartment(s): 1 of 4 patients (25%)
   2) Non-Prolift-treated compartment(s): 2 of 4 patients (50%)
   3) Both Prolift-treated and non-Prolift treated compartments: 1 of 4 patients (25%)

AT 1 YEAR

1. Stages 0-1: 4 of 7 patients = 57%
   a. 7 patients in total
   b. 3 patients without recurrence
   c. 4 patients with recurrence

      By recurrence in Prolift-treated or non-Prolift treated compartment(s)

      1) Prolift-treated compartment(s): 2 of 4 patients = 50%
      2) Non-Prolift-treated compartment(s): 2 of 4 patients = 50%

2. Stage 2: 16 of 56 patients = 29%
   a. 56 patients in total
   b. 40 patients without recurrence
   c. 16 patients with recurrence

By recurrence in Prolift-treated or non-Prolift treated compartment(s)
1) Prolift-treated compartment(s): 9 of 16 patients = 56%
2) Non-Prolift-treated compartment(s): 5 of 16 patients = 31%
3) Both Prolift-treated and non-Prolift treated compartments: 2 of 16 patients = 13%

3. Stage 3: 23 of 68 patients = 34%
   a. 68 patients in total
   b. 45 patients without recurrence
   c. 23 patients with recurrence
      By recurrence in Prolift-treated or non-Prolift treated compartment(s)
      1) Prolift-treated compartment(s): 14 of 23 patients = 61%
      2) Non-Prolift-treated compartment(s): 7 of 23 patients = 30%
      3) Both Prolift-treated and non-Prolift treated compartments: 1 of 23 patients = 4%
      4) Unknown type of anatomic recurrence: 1 of 23 patients = 4%

4. Stage 4: 3 of 5 patients = 60%
   a. 5 patients in total
   b. 2 patients without recurrence
   c. 3 patients with recurrence
      By recurrence in Prolift-treated or non-Prolift treated compartment(s)
      1) Prolift-treated compartment(s): 1 of 3 patients = 33%
      2) Non-Prolift-treated compartment(s): 1 of 3 patients = 33%
      3) Both Prolift-treated and non-Prolift treated compartments: 1 of 3 patients = 33%

C. Clinical failure by baseline stage of prolapse in Prolift-treated compartment(s) AT or BEFORE 1 YEAR
   1. Stage 0-1: 0 of 9 patients = 0%
   2. Stage 2: 8 of 72 patients = 11%
      By recurrence in Prolift-treated or non-Prolift treated compartment(s)
      1) Prolift-treated compartment(s): 4 of 8 patients = 50%
      2) Non-Prolift-treated compartment(s): 3 of 8 patients = 38%
      3) Both Prolift-treated and non-Prolift treated compartments: 1 of 8 patients = 12%
   3. Stage 3: 13 of 93 patients = 14%
      By recurrence in Prolift-treated or non-Prolift treated compartment(s)
      1) Prolift-treated compartment(s): 9 of 13 patients = 69%
      2) Non-Prolift-treated compartment(s): 3 of 13 patients = 23%
      3) Unknown type of clinical failure: 1 of 13 patients = 8%
   4. Stage 4: 2 of 6 patients = 33%
      By recurrence in Prolift-treated or non-Prolift treated compartment(s)
      1) Prolift-treated compartment(s): 1 of 2 patients = 50%

2) Non-Prolift-treated compartment(s): 1 of 2 patients = 50%

AT 1 YEAR

1. Stage 0-1: 0 of 7 patients = 0%
2. Stage 2: 7 of 56 patients = 12.5%
   By recurrence in Prolift-treated or non-Prolift treated compartment(s)
   1) Prolift-treated compartment(s): 4 of 7 patients = 57%
   2) Non-Prolift-treated compartment(s): 2 of 7 patients = 29%
   3) Both Prolift-treated and non-Prolift treated compartments: 1 of 7 patients = 14%
3. Stage 3: 7 of 68 patients = 10%
   By recurrence in Prolift-treated or non-Prolift treated compartment(s)
   1) Prolift-treated compartment(s): 5 of 7 patients = 71%
   2) Non-Prolift-treated compartment(s): 1 of 7 patients = 14%
   3) Unknown type of clinical failure: 1 of 7 patients = 14%
4. Stage 4: 2 of 5 patients = 40%
   By recurrence in Prolift-treated or non-Prolift treated compartment(s)
   1) Prolift-treated compartment(s): 1 of 2 patients = 50%
   2) Non-Prolift-treated compartment(s): 1 of 2 patients = 50%

D. Recurrence by type of Prolift procedure
   AT or BEFORE 1 YEAR
   1. Anterior Prolift
      a. Anatomic recurrence: 34 of 90 patients = 38%
         By recurrence in Prolift-treated or non-Prolift treated compartment(s)
         1) Prolift-treated compartment(s): 7 of 34 patients = 21%
         2) Non-Prolift-treated compartment(s): 24 of 34 patients = 71%
         3) Both Prolift-treated and non-Prolift treated compartments: 2 of 34 patients = 6%
         4) Unknown type of anatomic recurrence: 1 of 34 patients = 3%
      b. Clinical failure: 9 of 90 patients = 10%
         By recurrence in Prolift-treated or non-Prolift treated compartment(s)
         1) Prolift-treated compartment(s): 1 of 9 patients = 11%
         2) Non-Prolift-treated compartment(s): 7 of 9 patients = 78%
         3) Unknown type of clinical failure: 1 of 9 patients = 11%

   2. Posterior Prolift
      a. Anatomic recurrence: 20 of 35 patients = 57%
         By recurrence in Prolift-treated or non-Prolift treated compartment(s)
         1) Prolift-treated compartment(s): 8 of 20 patients = 40%
         2) Non-Prolift-treated compartment(s): 9 of 20 patients = 45%

3) Both Prolift-treated and non-Prolift treated compartments: 3 of 20 patients = 15%

b. Clinical failure: 4 of 35 patients = 11%
By recurrence in Prolift-treated or non-Prolift treated compartment(s)
1) Prolift-treated compartment(s): 1 of 4 patients = 25%
2) Non-Prolift-treated compartment(s): 2 of 4 patients = 50%
3) Both Prolift-treated and non-Prolift treated compartments: 1 of 4 patients = 25%

3. Total Prolift[702]
a. Anatomic recurrence: 36 of 59 patients = 61%
By recurrence in Prolift-treated or non-Prolift treated compartment(s)
1) Prolift-treated compartment(s): 36 of 36 patients = 100%
b. Clinical failure: 10 of 59 patients = 17%
By recurrence in Prolift-treated or non-Prolift treated compartment(s)
1) Prolift-treated compartment(s): 10 of 10 patients = 100%

AT 1 YEAR
1. Anterior Prolift
a. Anatomic recurrence: 18 of 76 patients = 24%
By recurrence in Prolift-treated or non-Prolift treated compartment(s)
1) Prolift-treated compartment(s): 5 of 18 patients = 28%
2) Non-Prolift-treated compartment(s): 10 of 18 patients = 56%
3) Both Prolift-treated and non-Prolift treated compartments: 2 of 18 patients = 11%
4) Unknown type of anatomic recurrence: 1 of 18 patients = 5%
b. Clinical failure: 7 of 76 patients = 9%
By recurrence in Prolift-treated or non-Prolift treated compartment(s)
1) Prolift-treated compartment(s): 1 of 7 patients = 14%
2) Non-Prolift-treated compartment(s): 5 of 7 patients = 71%
3) Unknown type of clinical failure: 1 of 7 patients = 14%

2. Posterior Prolift
a. Anatomic recurrence: 12 of 23 patients = 52%
By recurrence in Prolift-treated or non-Prolift treated compartment(s)
1) Prolift-treated compartment(s): 5 of 12 patients = 42%
2) Non-Prolift-treated compartment(s): 5 of 12 patients = 42%
3) Both Prolift-treated and non-Prolift treated compartments: 2 of 12 patients = 16%
b. Clinical failure: 3 of 23 patients = 13%

[702] By definition, all recurrent prolapse after the Total Prolift procedure occurs in a treated compartment.

By recurrence in Prolift-treated or non-Prolift treated compartment(s)
1) Prolift-treated compartment(s): 1 of 3 patients = 33%
2) Non-Prolift-treated compartment(s): 1 of 3 patients = 33%
3) Both Prolift-treated and non-Prolift treated compartments: 1 of 3 patients = 33%

3. Total Prolift
   a. Anatomic recurrence: 16 of 38 patients = 42%
      By recurrence in Prolift-treated or non-Prolift treated compartment(s)
      1) Prolift-treated compartment(s): 16 of 16 patients = 100%
   b. Clinical failure: 6 of 38 patients = 16%
      1) Prolift-treated compartment(s): 6 of 6 patients = 100%

IV. Complications
A. Overall: 124 of 146 patients = 85%

B. Mesh complications:[703]
NOTE: mesh contraction was not recorded; therefore, the proportion of patients with mesh complications is underestimated.
Mesh complications: 40 of 142 patients = 28%
1. Mesh erosion
   a. Overall: 15 of 142 patients = 10.6%
   b. By visit[704]
      1) 2w visit: 3 of 499 patients = 0.6%
      2) 6w visit: 6 of 474 patients = 1.3% (5 new, 1 persistent from 2w)
      3) 4m visit: 11 of 370 patients = 3.0% (7 new, 4 persistent from 6w)
      4) 1y visit: 1 of 142 patients = 0.7% (persistent from 6w and 4m)
2. Granulation tissue[705]
   a. Overall: 13 of 142 patients = 9.2%
   b. By visit
      1) 2w visit: 1 of 499 patients = 0.2%
      2) 6w visit: 4 of 474 patients = 0.8% (all new)
      3) 4m visit: 7 of 370 patients = 1.9% (all new)
      4) 1y visit: 1 of 142 patients = 0.7% (new)
3. "Problematic" vaginal incisions
   a. Overall: 10 of 142 patients = 7.0%
   b. By visit

[703] Based on the extent of missing data, I consider the data on mesh complications to be unreliable. For example, no new mesh erosions were entered between the 4-month and 1-year follow-up visits, which doesn't seem at all plausible.
[704] To avoid double-counting patients with persistent mesh erosion, only those patients with new mesh erosion were counted in the overall calculation.
[705] In 3 cases (patients #57, 260, 484), chemical cautery (silver nitrate or Monsel's solution) was performed without a diagnosis recorded; for the purposes of this summary, those cases were categorized as granulation tissue.

1) 2w visit: 11[706] of 499 patients
2) 6w visit: 2 of 474 patients (1 new with concomitant mesh erosion, 1 persistent from 2w[707])
3) 4m visit: 2 of 370 patients (both new, both with concomitant mesh erosion[708])
4) 1y visit: 0

4. Mesh revision: 3 of 142 patients[709]

C. Reoperation

AT or BEFORE 1 YEAR

1. Overall: 52 of 179 patients = 29.0% (52 patients with 54 reoperations)
2. Reoperation for prolapse: 19 of 179 patients = 10.6% (19 patients with 20 reoperations)
3. Reoperation for mesh complications: 5 of 179 patients = 2.8% (5 patients with 6 reoperations)
4. Reoperation for urinary complications: 25 of 179 patients = 14.0%
5. Other reoperations: 3 of 179 patients = 1.7%

AT 1 YEAR

1. Overall: 27 of 137 patients = 19.7% (27 patients with 29 reoperations)
2. Reoperation for prolapse: 14 of 137 patients = 10.2% (14 patients with 15 reoperations)
3. Reoperation for mesh complications: 4 of 137 patients = 2.9% (4 patients with 5 reoperations)
4. Reoperation for urinary complications: 8 of 137 patients = 5.8%
5. Other reoperation: 1 of 137 patients = 0.7%

D. Intraoperative and perioperative complications

1. Intraoperative complications: 15 of 514 patients = 2.9%
2. Perioperative voiding dysfunction: 50 of 513 patients = 9.7%
3. Hospital stay > 24 hours:[710] 22 of 486 patients = 4.5%

E. Postoperative complaints by follow-up visit

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[706] One patient had both a "problematic" vaginal incision and mesh erosion. She was not counted in this category for the overall percentage; she was counted in the mesh erosion category.

[707] Neither patient with persistent "problematic" vaginal incisions at 6w was counted in this category for the overall percentage.

[708] These 2 patients were not counted in this category for the overall percentage; they were counted in the mesh erosion category.

[709] One patient was not counted in this category for the overall percentage of mesh complications; she was counted in the prolapse reoperation category.

[710] Registry data for hospital length of stay were recorded in only 2 categories: 24 hours or less, and more than 24 hours.

Note: complaints were not defined.

Complaint	2 weeks N=504	6 weeks N=477	4 months N=378	1 year N=146
Overall[711]	48%	50%	58%	57%
Pain	18%	13%	8%	5%
Dyspareunia	---	1%	10%	8%
Urge/UUI	13%	20%	21%	16%
Constipation	11%	11%	14%	15%
Voiding dysfunction	6%	5%	4%	8%
SUI	7%	9%	14%	10%
OAB	8%	12%	14%	8%
UTI	1%	1%	0.5%	5%
Bulging	0.2%	0.4%	2%	6%
Defecatory dysfunction	---	0.2%	0.5%	---
Other	1%[712]	1.5%[713]	0.5%[714]	0.7%[715]
Unknown[716]	---	1%	0.6%	---
Patients with ≥ 1 complaint	77 of 504 = 15%	82 of 477 = 17%	83 of 378 = 22%	96 of 146 = 66%

X. Ethicon's Knowledge of the Risks of the Prolift, Internal Documents

Ethicon ignored valuable feedback from surgeons

Ethicon's representatives have testified consistently to the significant value of feedback and analysis from surgeons using the Prolift, other transvaginal mesh products, and even those who do not use mesh placed transvaginally. Scott Jones testified that this is a valuable component to Ethicon's development and ongoing evaluation of its medical devices:[717] David Robinson testified to this as well.[718] David Robinson confirmed that there was a benefit to speaking with surgeons who used mesh, as well as surgeons who did not use mesh for pelvic floor repair.[719] Despite the acknowledged value of this information, Ethicon routinely ignored or

[711] Overall is defined as the proportion of patients with 1 or more complaints.
[712] 2 patients with vulvar contact dermatitis; 1 patient each with hemorrhoids; bleeding/clotting; urethral prolapse; and vaginal cellulitis
[713] 2 patients with fecal incontinence; 1 patient each with fecal urgency, nocturia and enuresis, unresolved vaginal cellulitis, dysuria, and frequency
[714] 1 patient each with fecal incontinence; vulvar psoriasis
[715] Fecal incontinence in 1 patient
[716] Treatment with vaginal antibiotics, steroids, or lubricant without a symptom or diagnosis recorded
[717] Scott Jones dep., 683:19-684:13
[718] David Robinson dep., 92:14-94:11
[719] David Robinson dep., 573:16-575:18

failed to act on this information and failed to share the insights of surgeons with other surgeons on a widespread basis.

The Ethicon Expert Meetings in Germany

In a January 24, 2006 email,[720] Bob Roda expressed an interest in bringing a group of key opinion leaders and others to the "Hamburg institute" to demonstrate and discuss the requirements for the "next generation meshes." This was apparently in response to Ethicon's knowledge of the dangerous shortcomings of Prolene Soft ("over time contracts"), as expressed to Bob Roda at a TVM meeting in Paris: "The group is strongly looking forward to the potential for new materials for the Prolift product." Gene Kammerer responded on February 13, 2006 and indicated that at a meeting in Paris in 2004, "both Dr. Cosson and Prof. Jacquetin" had "expressed an interest in a new mesh to control and reduce scar formation." The meetings described by Bob Roda took place in June 2006 and February 2007.

The June 2, 2006 Ethicon Expert Meeting[721]

Professor Cosson discussed complications of pelvic floor surgery using mesh implants, including erosions, infection, and contraction. He stated that "Chronic pain is not a frequent complication – 1 case observed in 100 Prolift patients – yet it is the complication of most concern to surgeons." Despite Professor Cosson's assertion that chronic pain in 1% of patients is not frequent, even if that percentage is in fact accurate, this is a callous understatement of the devastating effect of chronic pain in the women affected. In later discussion, the group evidently agreed that chronic pain as a complication of permanent mesh implantation is untreatable.[722] It is important to consider the life-altering nature of chronic pain over the lifetime of women who have permanent Prolift mesh implantation, and the subsequent pain, suffering, and morbidity these women endure with multiple and aggressive surgical treatments in an attempt to address their symptoms. Professor Cosson may understand some of this, since he characterizes chronic pain as the complication of most concern to surgeons. Perhaps he should consider that this would also be one of the complications of most concern to patients.

Biological response to surgical mesh (Prof. Klosterhalfen)

Professor Klosterhalfen gave a presentation on the biological response to surgical mesh. He emphasized the huge surface area of meshes as representing more than 300 meters of suture. (Nevertheless, Ethicon's claims to certain characteristics of Gynemesh PS mesh rely on studies of Prolene suture, not mesh, which again serves to emphasizes the inadequacy if not irrelevance of such studies.) In addition, Professor Klosterhalfen stated that the body's response to polypropylene mesh is not transient, as claimed by Ethicon, but instead chronic: "Even after 20

[720] ETH.MESH.00585937-00585939
[721] ETH.MESH.00870466-00870476
[722] "Highlights from the discussion: Vaginal pain after implantation of meshes is rare, but feared, since there is not real treatment option (V. Lucente: prefer 20 recurrences or Erosions over 1 pain patient)"

years the tissue is still reacting to the mesh." He stated unequivocally: "There is no inert material." He also described that "every individual reacts different to a mesh." He went on to describe how fibrosis is responsible for complications in mesh usage; that critical pore size is at least 1 to 2 mm; and that scar formation is a combination of pore size, surface area of the implanted mesh, and type of polymer. Using a diagram, he depicted how, with large-pore mesh, fibrosis develops on the mesh fiber only, but with small-pore mesh, an interconnection between mesh pores due to fibrosis leads to mesh shrinkage.[723] He also described that meshes can cause nerve damage due to mechanical irritation, where the mesh bears on an adjacent nerve.

Professor Klosterhalfen described the process of mesh shrinkage associated with loss of water as in scar shrinkage that occurs normally without mesh. He described that mesh shrinkage of 20% translated into reduction of the implanted mesh area of 64%. He also described how tension of the mesh changes the pore size, which results in a change in elasticity of the mesh.

Based on discussion, the group established a list of unmet clinical needs and assigned these needs with numbers as to their priority, 10 being the most important. The most important unmet clinical need, clearly unmet with the Prolift product, was that there be no shrinkage and long-term contraction of the mesh, because severe contraction leads to dyspareunia, which leads to impaired sexual function.[724] The unmet clinical need, again clearly unmet with the Prolift product, that was given the next highest priority was that of no vaginal distortion, normal vaginal wall, and to maintain normal sexual function.[725]

The possible use of Ultrapro with the Prolift procedure was discussed by the group, evidently with a range of reactions. It was recorded that Dr. Lucente fully supported the idea, but that Professors Cosson and Jacquetin would prefer clinical data supporting its use first.[726]

The February 23, 2007 Ethicon Expert Meeting[727]

Approximately 8 months later, Ethicon sponsored another expert meeting to discuss meshes for pelvic floor repair. Peter Meier gave an introduction and update of Project "LIGHTning" (Ethicon's internal name for what became the Prolift + M Systems), which was in the development phase at that point. He reported that the team had achieved discovery work successfully, and they believed that Ultrapro was the most promising available mesh for pelvic floor repair. It is important to note the use of the term "available" here; Ethicon did not independently research or develop the Ultrapro mesh for use in transvaginal prolapse surgery. As

[723] This diagram depicted the safe interconnection between mesh fibers in large-pore mesh and the unsafe "fibrotic interconnection" with small-pore mesh.
[724] Summary of unmet clinical needs: Priority = 10: No shrinkage/no long-term contraction; Fibrosis reduction; Severe contraction leads to Dyspareunia leads to decreased sexual function
[725] Summary of unmet clinical needs: Priority = 8: No vaginal distortion, normal vaginal wall, maintain sexual function, normal sexual function
[726] The usage of Ultrapro in Prolift was fully supported by V. Lucente. M. Cosson and B. Jacquetin like the idea, however would like to have some clinical data before supporting it.
[727] ETH.MESH.02017152-02017158

previously noted, at that time, before its use in the Prolift + M Systems, Ultrapro mesh was marketed for use by general surgeons in hernia repair. Ethicon chose Ultrapro for commercial reasons, "in order to maintain market share," and because Ultrapro was readily available to use as a substitute for the Gynemesh PS mesh in the Prolift Systems.[728] In fact, as noted above, Ultrapro had been considered for use as the mesh to be used in the Prolift Systems, but Ethicon chose to pursue marketing the Prolift Systems with Gynemesh PS mesh. Peter Meier also discussed that further animal and clinical data was needed to substantiate Ethicon's discovery work related to the Ultrapro mesh before launch of a commercialized product.

Dr. Arlt gave a presentation on the use of Ultrapro mesh in hernia surgery. He reported that there were "almost no problems like pain, shrinkage, or recurrences with modern lightweight meshes in hernia surgery." He described that mesh shrinkage was not an issue in hernia surgery as long as the mesh was large enough to cover the defect sufficiently. He warned, on the other hand, that "a bigger mesh will automatically lead to more foreign body and tissue reaction." Professor Klosterhalfen described that the textile structure of the mesh, specifically the pore size and knitted construction, was more important than the area weight, and that terms like "light-weight" and "heavy-weight" when referring to mesh "may be misleading." Professor Cosson questioned whether polypropylene was the best material, as fractures have been observed in polypropylene over time.

Kirsten Spychaj, of the Hamburg mesh development facility, gave a presentation on "Factors related to mesh shrinkage"[729] and reported that, in pelvic floor surgery, shrinkage seems to be more important than in hernia surgery. It is important to note that it is not possible for mesh to overlap the "defect" by several centimeters in transvaginal mesh prolapse surgery, as has become standard in hernia surgery. This presentation presented a succinct summary of the mesh contraction problems arising from the use of the Prolift, for example:

> Pore size
> - Small porous meshes (<1mm) lead to "fibrotic bridging" → increased shrinkage
> - Large porous meshes allow for a better and faster tissue ingrowth → less shrinkage/contraction
>
> …
>
> Intensity of FBR (foreign body reaction)
>
> - Quality and quantity of FBR are directly related to mesh type

[728] ETH-60382, Project Lightning Commercialization Strategy, 8-8-2007: "To continue meeting market needs, Ethicon Women's Health & Urology knows it is critical to integrate a lighterweight pre-shaped synthetic mesh in the Prolift system in order to maintain market share. Looking at quickly available synthetic meshes within the Ethicon Products portfolio, Ultrapro product has been identified as the preferred choice because of its characteristics and lower density."

[729] ETH.MESH.02092787

- Excessive FBR → massive scar plate → more shrinkage
- Total prevention of FBR is not advisable since it is needed for a stable scar tissue

…

Individual/patient related factors

- Extent of shrinkage is sometimes different between individuals (even if same mesh/technique is used)
  Note that this is an explicit acknowledge that complications, such as mesh shrinkage, are NOT due to surgical technique and vary between individuals on the basis of other factors.
- Regarding the extent of the FBR there are "high and low responders"
- May be genetically determined

…

"The ideal mesh" in theory

- Lightweight material (partly absorbable)
- Pore size >1 mm (avoid "fibrotic bridging")
- Mild but not excessive FBR
- Swift and adequate tissue integration warranted
- Position maintenance to prevent early displacement

In discussion about a model for pelvic floor repair, it was stated that no adequate animal model exists, and there was no agreement as to whether an abdominal wall model might be a better solution. An objection raised to the abdominal wall model was that there is no real (parietal) fascia in the pelvic floor. Professor Cosson stated that polypropylene meshes might not be improvable in terms of shrinkage, and that a completely new material may be needed for transvaginal mesh prolapse surgery. It was stated that vaginal elasticity is very important; the vagina must be able to move. The group felt that there was a:

> **"Need to learn more about special anatomic features in the vaginal region (may be done with cadavers); Vagina consists of muscles and epithelium, here is a lot of movement in interface "epithel/muscle" (completely different from abdominal wall); vagina is a contractile organ, lots of movements occur only during sexual activity."**

The summary of unmet clinical needs that was generated at the June 2006 was again confirmed without any changes, underscoring the fact that the Prolift product and procedure was not meeting the identified needs.

Despite Ethicon's ongoing knowledge about the dangerous shortcomings of Prolene Soft mesh, starting before the Prolift was ever launched, Ethicon used Prolene Soft mesh (renamed as Gynemesh PS mesh) in the Prolift and continued to market this unreasonably dangerous device and procedure. They did so despite their own internal knowledge of these dangers, developed through close interaction with the French TVM group and others; choosing to market the device as a safe, "revolutionary" device while knowing that a significant number of women would suffer serious and in some cases, untreatable, complications including and as a result of mesh contraction, erosion, and others.

Presentations and Papers

Beginning before the Prolift was launched and continuing thereafter, a series of internally generated presentations and papers demonstrated Ethicon's awareness of the problems with the use of mesh to repair the pelvic floor in general, and the use of the Prolift procedure and the Prolene Soft/Gynemesh PS mesh in particular. This information was not adequately taken into account in Ethicon's decision to market the medically unsafe Prolift.

Meshes in Pelvic Floor Repair, Prepared by Brigitte Hellhamer, Ethicon GmbH, R&D Europe, June 6, 2000[730]

This paper contains numerous important statements demonstrating the state of knowledge of the research and development scientists tasked with developing and testing mesh materials.

> "This report is based on findings from in-house data, from 62 publications on pelvic floor repair, including studies on the use of mesh implants, and from conversations and interviews with 23 surgeons from US, UK, Sweden, Finland, France, Italy, The Netherlands and Germany.
>
> …
>
> The rationale of colporrhaphy technique is to repair the defect by creating a thin scar which will then restore the original function of the tissue. To buttress the repair additionally mesh implants – non-absorbable, composite and absorbable – have been used for repair of prolapse stage III or IV for second or more recurrence, but are generally not recommended for primary repairs, because there is concern to use mesh implants in view of the **observed mesh-related complications** (22210):
>
> - Erosions in abt. 10% (more when ePTFE was used)
> - After sling procedures up to 35 % removal rate (Gore-Tex)
> - 10% sinus tract formation (Gore-Tex)
> - Urethral erosion 4% (Marlex)

[730] ETH.MESH.03924557-03924561

- Fistula (1.4%)
- Mesh removal 6%
- Overall revision and removal rate among 961 synthetic suburethral slings of 7,3% (22210).
- Overall revision and removal rate among 592 sacrocolpopexies of 2.7%

…

Desirable mesh product features

Anterior and posterior vaginal wall repair:

- Multidirectionally stretchable to conform to bladder filling after surgery to reduce tension on the fixation sutures.
- Cuttable without releasing fibres after cutting
- No sharp edges after cutting
- Able to be sutured
- Relatively large pore size (similar to Vypro or Vypro II)
- Minimum amount of foreign body mass
- Minimum foreign body reaction
- Tissue incorporation with little retraction (ideally, the mesh would induce formation of neo-fascia and then absorb)
- **Mechanical strength: The in vivo forces and exerted strains on pelvic floor repair during the postoperative period are not known. No studies on this subject were identified through literature search or interviews with experts. However, experimental and clinical data are available on Vypro mesh for incisional hernia repair. First confidential verbal reports of surgeons using Vypro for cystocele repair suggest that its mechanical characteristics comply with requirements of anterior and posterior vaginal wall reconstruction.**
- Handling: easily conforming to implant area. Edges should be smooth. Mesh should not roll at the edges.

…

Success factors of the ideal treatment in pelvic floor repair

Less than 20% recurrence
Less than 10% erosions
Access allowing simultaneous or later correction of associated stress incontinence
Minimally invasive – reduced trauma
Simple to perform
Minimal dissection

Scarce resection of healthy tissue
Repositioning normal anatomy
Painfree postoperatively
Tension-free
No obstruction (no dyspareunia)
No overcorrection (could cause voiding problems or fecal obstruction)
Short operation time
Fast patient recovery
Ambulatory procedure

The interviews with the surgeons provide specific information based on actual clinical experience. For example:

Surgeon 1 has the following annual procedures at his hospital:

270 abdominal colposuspension (Burch) for stress urinary incontinence treatment
80 TVT for stress incontinence in older patients (abt. 60 and older)
81 180 vaginal repairs (80 for cystocele, 100 for rectocele)
90 sacrocolpopexies for vaginal prolapse
…
He would never use mesh material for anterior vaginal wall repair, because he thinks this is a very delicate area, with the nearness of the bladder neck and a risk of the mesh eroding into the urethra, bladder neck or bladder.
…
Surgeon 1 emphasizes that the pelvic floor pathology is a challenging area for the surgeon. With his awareness of the need to improve surgical techniques in pelvic floor repair, he has been trying to improve his technique for the past 19 years and yet has not reached a stage of satisfaction with his results so far.

…

Surgeon 3 has done 200 pelvic floor repairs, anterior, posterior, combinations of both, and sacrocolpopexy, for the past two years, first using Gynemesh, then switching to Vypro after he had become aware of this new mesh.

Gynemesh: is perceived as too bulky and rigid. **Also, when cutting the mesh, small particles are released that migrate through the vaginal wall causing pain during intercourse.** Surgeon 3 thinks that Gynemesh will never be a success, also for cost reasons. Many surgeons would buy the cheaper Prolene mesh, cut it themselves and then resterilize it. This could obviously not be done with the Vypro mesh.
…
Surgeon 11 has carried out a study using Gynemesh for repair of isolated cystocele, without other concomitant pelvic floor defects… Surgeon 11 likes the

> Gynemesh, but he thinks a thinner mesh could be more acceptable to surgeons. He could not tell if he would prefer Vypro or just another thinner mesh such as Soft Prolene Mesh. Both concepts seem plausible to him. **It is important that the mesh can be cut to individual sizes, it must not fray nor release particles.**
>
> …
>
> **Surgeon 14** stated he will not use any mesh for pelvic floor repair. In the past, his colleagues were quite enthusiastic about meshes. Later on, there was the disappointment, with meshes leading to erosion and extrusion. He has no experience himself. This is what he heard from other surgeons.
>
> …
>
> **Surgeons 22 and 23** were both mildly positive in the sense that they see potential value in a concept of using mesh for pelvic floor repair. They trust synthetic materials very much and in no case prefer biologic materials. Both would immediately use a thin pliable synthetic mesh. **Both mentioned that the mesh needs to have some degree of flexibility to comply with the movements of the pelvic floor.**

Review of Surgical Techniques Using Mesh, David Robinson, M.D.[731]

This presentation ultimately advocates for the transvaginal placement of mesh, but there are several important points made. The second slide provides a quote attributed to Dr. Jim Raders and Vince Lucente: "Reconstructive pelvic surgery using only native tissue perhaps can be considered in the twilight of its era." The note under the slide states that "The dawn of enhanced support will be the selective or routine use of mesh to reinforce our repairs and subsequently decrease our reoperation rate." Unfortunately, what should have been anticipated by Ethicon and mesh proponents like Dr. Robinson was that the reoperation rate would not only NOT decrease but actually increase substantially because of the high complication rate of mesh-based vaginal prolapse surgery and the frequent requirement for surgery, and multiple surgeries, to address those complications.

In the tenth slide, Dr. Robinson misrepresented the data from the same 3 references[732] that Ethicon has relied on to exaggerate the failure rate of traditional vaginal prolapse surgery, in order to falsely bolster the claim that mesh use in vaginal prolapse repair is justified. See

[731] ETH.MESH.00396836, 2004

[732] Clark AL, Gregory T, Smith VJ, Edwards R. Epidemiologic evaluation of reoperation for surgically treated pelvic organ prolapse and urinary incontinence. Am J Obstet Gynecol 2003; 189(5): 1261-1267; Marchionni M et al. True incidence of vaginal vault prolapse. Thirteen years of experience. J Reprod Med 1999; 44: 679-684; Olsen AL et al. Epidemiology of surgically managed pelvic organ prolapse and urinary incontinence. Obstet Gynecol April 1997; 89:501-506.

Medical Literature Review, for a detailed discussion of how Ethicon has miscited these same 3 articles year after year.

Midway through the PowerPoint presentation is the 15th slide titled: "Why has the field of Gynecology not adopted the routine use of meshes?" The first reason given is that: "Early clinical experience was met with an unacceptably high mesh complication rate," and cites to rates of 6-25%, 3-12%, and 6-12%. If those rates are unacceptably high, then the rates with the Prolift are unacceptably high, since the Prolift complication rates are even higher. The next page makes a key point that was not adequately taken into account by Ethicon at any time:

The Vagina is NOT the Abdomen

(nor similar to any other surgical environment)

The 16th slide of the PowerPoint presentation lists multiple reasons why the Prolift concept was never viable:

Issues in the Use of Synthetics in Pelvic Reconstructive Surgery

Unique issues to the vagina in the placement of large meshes

- **Cannot be sterilized**
- **Relatively thin overlay with no real fascial layer**
- **Attachment sites are difficult to access**
- **The three dimensional architecture and various vector forces are complex**
- **Subject to great forces with little or no bony (and often pelvic floor muscle) reinforcement**
- **Must remain pliable for filling and emptying of pelvic organs and maintain the capacity for sexual function**

Although the last slide in this presentation made the claim that "only recently has the material science addressed the unique requirements for mesh use in the vagina," the mesh promoted for use in transvaginal prolapse surgery has not been "addressed" by material science at all; it was a hernia mesh, Prolene Soft mesh, that was renamed as Gynemesh PS mesh and marketed for use in vaginal prolapse repair. Even more importantly, the unique issues related to vaginal placement of large meshes, as listed above, have emphatically NOT been addressed for the use of Gynemesh PS mesh (or likely for the use of any other permanent mesh), as unequivocally demonstrated by the very high rate of complications following the use of Gynemesh PS mesh for vaginal prolapse repair.

Clinical Evaluation Report, Mesh Erosions, Peter Meier, M.D.
Principal Scientist, Johnson & Johnson Medical GmBH, September 13, 2010[733]

[733] ETH.MESH.00869977-00870098

An ideal mesh material should have the following characteristics:

- Sterile
- Does not elicit any immune reaction
- Non-carcinogenic
- Allow tissue ingrowth
- Mechanically durable
- Inexpensive
- Convenient and easy to use

…

Mesh related complications

While the advantages of synthetic meshes are evident, specific concerns regarding their use which can seriously compromise the patient's health and quality of life have been reported in the literature. Once the mesh material has been implanted in the body, the host immune system reacts to the introduction of this foreign material and covers the material with a biofilm. This triggers a complex series of host-to-implant material interaction. A typical inflammatory response is elicited which involves activation of the complement system, binding the antibodies, leukocyte formation, blood clotting, and fibrinolysis activation. This is followed by an acute inflammatory phase and a chronic inflammatory phase resulting in foreign body reaction; formation of granulation tissue with fibroblasts, macrophages, and neovascularization; and eventually foreign body giant cells and fibrosis.

MESH RELATED COMPLICATIONS MAY BE ASSOCIATED WITH THE MESH MATERIAL USED FOR REINFORCEMENT OR THE SURGICAL PROCEDURE ITSELF.[734] Mesh material related adverse events include infections, erosions, extrusions, mesh shrinkage, vaginal granulation tissue, sinus formation, abscess, fistulas or osteomyelitis. Complications reported due to the surgical techniques including bleeding, hematoma formation, bladder and bowel injury, adhesions and obstructive ileus. Additionally, functional problems such as de novo urgency, urge incontinence, dyspareunia and non-specific pelvic pain may also be observed in certain patient groups.

…

[734] This is an explicit recognition that complications asserted with the mesh or the procedure are related to the Prolift.

Of all these complications, mesh erosion remains a major cause of concern in the use of meshes in pelvic reconstructive surgery. Several factors contributing to the wide range of erosion rates prevalent in pelvic floor repair include patient characteristics such as age, estrogen deficiency, obesity, uncontrolled diabetes, operative technique, implant size, and the specific properties of the mesh material, such as pore size, stiffness, elasticity and basic tissue compatibility.

…

Interaction at the host tissue-mesh interface

The reaction of tissues to mesh material at the host tissue-mesh interface can be divided into 4 types:

- Minimal response with a thin layer of fibrosis around the implant;
- Chemical response with a severe and chronic inflammatory reaction around the implant;
- Physical response with an inflammatory reaction to certain materials and the presence of giant cells; and
- Necrotic tissue: a layer of necrotic debris is produced resulting from in situ exothermic polymerization.

The ideal mesh used for reconstructive surgery should elicit minimal inflammatory and cellular response followed by vascular and fibroblastic infiltration. The promotion of fibrous growth around the mesh without tissue infiltration is associated with the phenomenon of ‘encapsulation’ which decreases the efficacy and increases the risks of erosion as the mesh is not being incorporated into host tissues.

…

Surface area of mesh

The amount of foreign body reaction increases with the amount of surface of the foreign material being exposed to the host. It has been noted that the smaller the surface of the implant, the less reaction observed and reactions will be proportional to the area of contact with the foreign body. The area of contact between the foreign substance and the exposed tissue is an important determinant of the tissue reaction. In general, less foreign material may lead to better host acceptance and tissue incorporation. Therefore, a thinner mesh combined with less material per given area reduces the risk of erosion.

…

Publications identifying patients with higher risk of erosion

Although the exact etiology of vaginal erosion is not known, there are various predisposing factors that may contribute to mesh erosion. Study of the literature shows that there are certain groups of patients who are more susceptible to mesh erosions after pelvic floor repair surgery. This section deals with factors that put a patient at higher risk of erosion as compared to the others.

- **Patients with previous or concomitant hysterectomy procedures**
- **Vaginal wall imbrications with silk sutures**
- **Smoking/tobacco users**
- **Patient age**
- **Other important risk groups**

  Women who:
  - Have poorly controlled diabetes mellitus
  - Are obese
  - Have a prior history of irradiation
  - Are immune compromised
  - Have sexual intercourse early after vaginal surgery

…

Surgical Management

Residual infected mesh after a failed partial excision requires a second excision generally via laparotomy, and usually represents **a difficult surgical dilemma as recurrent erosions are associated with chronic morbidity including chronic infection, sinus tracts, abscess and fistula formation.**

…

With the current widespread use of mesh materials to reinforce pelvic floor reconstructive techniques, it is imperative for surgeons to be familiar with potential complications related to the materials and proper management of these complications. **When used by an experienced and advanced pelvic surgeon with an in-depth knowledge of female pelvic anatomy in the proper clinical situation with appropriate patient selection, the benefits of these meshes outweigh the risks.**[735] **Complications still do occur, even in the most**

[735] These are far narrower than the criteria set forth in the Prolift IFU or patient brochures.

> **experienced surgeons hands**, but again these seem to be minimal when surgeons utilize proper techniques. Proper diagnosis and management of complications as well as effective post-operative patient care play an important role in improving the quality of life of the patient.

Despite Ethicon's claim, as described above, that complications "seem to be minimal when surgeons utilize proper techniques," this is clearly contradicted by the evidence cited throughout this report, particularly in the medical literature when studies have been performed without the pervasive financial bias seen in all work sponsored by Ethicon and its highly paid consultants. It is certainly true that "proper diagnosis and management of complications" are important in improving care for patients; however, Ethicon itself inexplicably refused to provide physicians with critically important information about the Prolift procedure and permanent Prolift mesh implantation that would allow those physicians to do exactly that, properly diagnose and manage complications in patients. As discussed in detail elsewhere in this report, just a few examples include Ethicon's failure to inform physicians of the need for and appropriate timing of cystoscopy and rectal examination during the Prolift procedure, in order to properly diagnose and manage complications with the least harm possible to patients.

Biomech[a]nical consideration for Pelvic floor mesh design[736]
Jurgen Trzewik, Senior Scientist and Christophe Vailhe, Principle Scientist
February 16, 2011

> The Introduction of this document states that:
> … the ideal mesh for prolapse[e] repair which mimics precisely the biomechanical needs of the pelvic floor region has not been developed. A recent major focus of mesh development and research is the patient's quality of life. Pain and discomfort can result from stiff mesh that were [sic] originally designed for hernia surgery and "over-engineered" to exceed the burst strength of the abdominal wall at the cost of losing compliance. Although limited data suggests that, in terms of anatomical and biomechanical outcomes, synthetic polypropylene meshes are superior to biologic meshes, **there is significant evidence that the complications associated with synthetic meshes can cause significant morbidity including infection, erosion, exposure, and pain**. In addition, the vaginal tissue to be augmented is often structurally compromised, atrophic, and devascularized. Such poor tissue quality increases the risk of poor tissue incorporation into the mesh potentially resulting in suboptimal healing and mesh exposure or erosion into an adjacent viscous [sic]. **Moreover, there is evidence that meshes shrink in vivo leading to increased stiffness, pain, and poor restoration of the normal properties of the vagina[']s] compliance. Research has demonstrated that bioprosthetic mesh implantation results in a scarring**

[736] ETH.MESH.02185584-02185605

> **reaction and subsequent decreased compliance.** An ideal quality of prosthetic mesh would be to mimic the compliance of the supported tissue thereby resulting in more comfort and function after implantation. To be able to define the most appropriate design parameters for the next generation of pelvic floor prosthesis it is important to generate an advanced understanding of the pelvic floor biomechanics and associated mechanical boundary conditions (e.g. pelvic floor forces).

Ethicon has known for years that the forces affecting the pelvic floor are unknown, and it has never initiated research that would "generate an advanced understanding" of those forces in order to "be able to define the most appropriate design parameters for the next generation of pelvic floor prosthesis." In fact, Ethicon has never designed a mesh specifically for the pelvic floor at all; it has simply taken its meshes used for hernia repair and transferred them to prolapse repair. As stated clearly above, use of "stiff mesh that were [sic] originally designed for hernia repair and 'over-engineered'" for use in prolapse repair has resulted in patients suffering "pain and discomfort." Ethicon presented the information in the introduction of this document as it were stating something previously unknown, when the fact is that nothing in the above paragraph is new; Ethicon has been aware of all this information for years.

Investigating Mesh Erosion in Pelvic Floor Repair, PA Consulting Group[737]
May 18, 2011

> Mesh erosion in pelvic floor repair is a complication affecting 0-20% of patients.
>
> - Johnson and Johnson Medical provide knitted meshes for use in pelvic floor repair surgical procedures.
> - A review of a substantive body of clinical studies report that 0-20% of pelvic floor repair procedures suffer post surgical complications of 'mesh erosion'; a condition in which the mesh migrates from its original location, ultimately resulting in exposure of the mesh
>   - This can be associated with pain, irritation and infection
> - J&J have investigated this issue – including an extensive literature search – to evaluate the causes of mesh erosion and hence to identify potential approaches to eliminating or reducing the incidence
> - However, it has proved difficult to generate a clear answer as there are many variables which potentially affect the incidence of mesh erosion
>
> …

[737] ETH.MESH.02589032-02589079

Mesh erosion is complex and the clinical studies do not give a clear picture, due to the diversity of variables.

- The causes of mesh erosion are not well understood and may be triggered by mechanical tissue damage and/or by immunological rejection processes
  - Can occur along suture lines, mesh fold lines, rough edges
  - Can cause migration and bunching-up of the mesh

- There are many studies reporting the incidence of mesh-related infections; and erosion figures vary widely depending on the reporting author and the study
- Non-specific pelvic pain, persistent vaginal discharge or bleeding, dyspareunia, and urinary or fecal incontinence are the most common manifestations of vaginal mesh-related infection

…

Mesh erosion is lower with PP [polypropylene] meshes used in trans-abdominal surgery than in trans-vaginal surgery.
…
Implants placed via the abdominal route suffer lower rates of mesh erosion than those placed during vaginal surgery and may show lower infection rates*
…
*intuitively trans-vaginal surgery would be expected to show higher infection rates and this was confirmed by the surgeons interviewed and reporting authors

…

Surgeon skill may be an important factor in the risk of mesh erosion
…
- Leading UK gynecologists who sub-specialise in vaginal floor repair tend to be conservative in their use of mesh, using it in limited cases (often only for revisions)

  - If they do use mesh, they tend to reject the trans-vaginal kits with the trocars and operate trans-abdominally, cutting out a piece of mesh to size and shape

  - None of those interviewed had problems with mesh erosion, although they had observed it

- The interviewees speculated that a significant contributor to observed erosion rates is insufficiently skilled surgeons using the trans-vaginal kits and essentially inserting the trocars "blind"

…

There are many variable factors which have potential to influence mesh erosion

- Materials and method of production define the mesh attributes and characteristics. These in turn influence the behavior of the mesh once implanted. Mesh variables include:
  - Pore size – macro vs. micro
  - Filament construction; multifilament vs. monofilament
  - Mesh density (weight/unit area)
  - Pore depth
  - Surface area
  - Rigidity (resulting from filament gauge used and construction)
  - Elasticity
  - Filament surface effects, character, composition, extractables

- **There are other variables which can impact on mesh behavior, including**
  - **Surgical technique and approach**
  - **Surgical procedure**
  - **Patient characteristics and co-morbidities**
  - **Individual response**

…

Vaginal surgery has a higher risk of mesh erosion than abdominal surgery.

…

A high level meta-analysis of the data in the J&J literature search[738] was conducted and erosion rates from all studies therein were tabulated. Trans-vaginal implantation appears to show higher erosion rates than trans-abdominal surgery.

…

PA concludes that trans-abdominal surgery has lower complication rates than trans-vaginal surgery.

…

[738] Ref J&J literature search; Clinical Evaluation Report Mesh Erosions, Peter Meier September 2010

Mesh production processes could influence erosion risk

…

- High magnification pictures of filaments within a random sample of finished products show a number of surface effects (note also images on the following slides)
- It is not certain where in the production process these artefacts [sic] are generated; perhaps extrusion/winding and scouring
- We cannot discount the possibility that this type of artefact contributes to the potential for undesirable clinical outcomes
- There may be other variables in the process that also produce variations in the finished product that in turn, might influence the behavior of the implanted mesh e.g. heat sealing

Gynemesh PS filaments exhibit artefacts on the surface[739]

…

Polypropylene can suffer from degradation following implant

- **... it [polypropylene] is subject to degradation; a process which initiates after a few days post implantation in animal studies**

Similar to Ethicon's practice of soliciting feedback from experienced Prolift users and then ignoring it, within the space of 3 months, Ethicon commissioned two extensive literature reviews on the subject of mesh erosion (exposure), each report with a detailed evaluation and summary of the medical literature and other sources; yet, what Ethicon did with all this information is unknown. What is known is that Ethicon continued to fail to disclose such material knowledge to physicians and patients; Ethicon failed to update any of its Prolift-related materials with regard to any of this information.

Life Events and Prolift Mesh-Related Complications

As previously noted, Prolift mesh implantation carries a life-long risk of mesh-related complications. Beyond that, the ongoing presence of Prolift mesh in the pelvis carries additional risks, including the risk of complications that occur as a result of otherwise unrelated events and the risk of interfering with the interpretation of imaging studies performed for unrelated conditions. In addition, the ongoing presence of Prolift mesh outside of the pelvis, passing through tissues unrelated to the primary process of prolapse, introduces an entirely new category of complications to the hip, thigh, and groin. There are no such risks after traditional vaginal prolapse surgery.

Although the pathophysiology of vaginal mesh exposure is not fully understood, studies have begun to identify risk factors that increase the likelihood of vaginal mesh exposure. Some factors that increase the frequency of vaginal mesh exposure are associated with the surgery

[739] Several pictures demonstrated artifacts on the Gynemesh PS mesh filament surface.

itself, including increased burden of Prolift mesh implantation (total versus anterior or posterior),[740] and concomitant vaginal hysterectomy, especially in conjunction with "T"-shaped vaginal incisions[741] (although others have suggested that technique modifications are sufficient to address this association[742]). One other mesh-related complication, mesh retraction, has been associated with an increased frequency of vaginal mesh exposure.[743]

Some risk factors that increase the frequency of vaginal mesh exposure are related to the patients' medical and surgical history, including smoking,[744,745] multiparity,[746] previous vaginal reconstructive surgery,[747] and somatic inflammatory disease such as rheumatoid arthritis.[748] In one study, sexual activity was a risk factor for late mesh exposure.[749] The data on the association between age and the risk of vaginal mesh exposure are inconsistent, with some studies identifying increasing age as a risk factor,[750] while other studies identify decreasing age as a risk factor for vaginal mesh exposure.[751] The issue of age and risk for vaginal mesh exposure may be influenced by a number of factors, including sexual activity and extent of prolapse. As noted above, sexual activity was identified by one study as a risk for vaginal mesh exposure, and younger women are more likely to be sexually active. Regarding the extent of prolapse, since the vaginal epithelium tends to toughen and thicken with more advanced prolapse, this may provide a more substantial layer of tissue overlying the mesh implant and may explain the association

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[740] Withagen MI et al. Risk factors for exposure, pain, and dyspareunia after tension-free vaginal mesh procedure. Obstet Gynecol 2011; 118(3): 620-636.

[741] Collinet P et al. Transvaginal mesh technique for pelvic organ prolapse repair: mesh exposure management and risk factors. Int Urogynecol J 2006 Jun; 17(4): 315-320. Epub 2005 Oct 15.
Sayasneh A, Johnson H. Risk factors for mesh erosion complicating vaginal reconstructive surgery. J Obstet Gynaecol 2010; 30: 721-724.

[742] Murphy M et al. Vaginal hysterectomy at the time of transvaginal mesh placement. Female Pelvic Med Reconstr Surg 2010; 16: 272-277.

[743] PLTMEDLIT01656. Caquant F et al. Safety of Trans Vaginal Mesh procedure: Retrospective study of 684 patients. J Obstet Gynaecol Res 2008; 34 (4): 449-456.

[744] Withagen MI et al. Risk factors for exposure, pain, and dyspareunia after tension-free vaginal mesh procedure. Obstet Gynecol 2011; 118(3): 620-636.

[745] Elmer C et al. Risk factors for mesh complications after trocar guided transvaginal mesh kit repair of anterior vaginal wall prolapse. Neurourol Urodyn 2012 Apr 19. Doi: 10.1002/nau.22231 Epub ahead of print.

[746] Elmer C et al. Risk factors for mesh complications after trocar guided transvaginal mesh kit repair of anterior vaginal wall prolapse. Neurourol Urodyn 2012 Apr 19. Doi: 10.1002/nau.22231 Epub ahead of print.

[747] Sayasneh A, Johnson H. Risk factors for mesh erosion complicating vaginal reconstructive surgery. J Obstet Gynaecol 2010; 30: 721-724.

[748] Elmer C et al. Risk factors for mesh complications after trocar guided transvaginal mesh kit repair of anterior vaginal wall prolapse. Neurourol Urodyn 2012 Apr 19. Doi: 10.1002/nau.22231 Epub ahead of print.

[749] Kaufman Y et al. Age and sexual activity are risk factors for mesh exposure following transvaginal mesh repair. Int Urogynecol J 2011; 22: 307-313. Epub 2010 Sep 30.

[750] Deffieux X et al. Vaginal mesh erosion after transvaginal repair of cystocele using Gynemesh or Gynemesh-Soft in 138 women: a comparative study. Int Urogynecol J 2007 Jan; 18: (1): 73-79. Epub 2006 Jan 4.

[751] Kaufman Y et al. Age and sexual activity are risk factors for mesh exposure following transvaginal mesh repair. Int Urogynecol J 2011; 22: 307-313. Epub 2010 Sep 30. Late mesh exposure associated with younger age with an odds ratio of 1.99 for each decade of younger age.
Pacquee S et al. Complications and patient satisfaction after transobturator anterior and/or posterior tension-free vaginal polypropylene mesh for pelvic organ prolapse. Acta Obstet Gynecol Scand 2008; 87: 972-974.

between more advanced prolapse and lower frequency of vaginal mesh exposure seen in one study.[752]

Of the few risk factors for vaginal mesh exposure after permanent Prolift mesh implantation identified so far (which is by no means a complete understanding), most are not modifiable. Modification of the Prolift technique may lessen the frequency of vaginal mesh exposure, but this has not yet been replicated outside of the one study that reported it.

The issue of age in association with vaginal mesh exposure is a significant cause for concern; obviously, all women after the Prolift procedure will continue to age until death intervenes. It is apparent that aging women will be at increasing risk for the development of vaginal mesh exposure, particularly in combination with vaginal atrophy due to estrogen deficiency after menopause. In addition, this risk may be increased as other medical conditions develop, for example, circulatory deficiencies that reduce blood flow to the pelvis. As previously described, due to the chronic inflammatory and foreign body reaction, Prolift mesh causes extensive tissue damage including damage to blood vessels and nerves that normally ensure proper nourishment of the surrounding tissues. Add to this, for example, the development or worsening of atherosclerosis (hardening and narrowing of the arteries), a common circulatory disease, and it can be easily seen how the risk of Prolift mesh-related complications will increase over time. As women's tissue ages over years and decades, and as women develop relevant co-morbidities such as circulatory disease and diabetes, their risk of mesh erosion and exposure will increase, and then at a more advanced age, at a time when any surgery carries increased risk, they will face the need to have invasive, complex surgery to attempt to remove the Prolift mesh from their bodies. This increasing risk will manifest itself in the development of erosion and other Prolift mesh-related complications in women who have already suffered complications and in those who have suffered none to date. Ethicon has never addressed or warned physicians or patients about this "ticking time bomb."

In addition, other life events will take place in women after the Prolift procedure that may increase their risk of vaginal mesh exposure and other Prolift mesh-related complications. As one example, the lifetime risk of a woman developing any type of invasive cancer is 38%;[753] with that risk comes the likelihood of requiring chemotherapy and/or radiotherapy. Ethicon has never studied what will happen in women after Prolift mesh implantation during or after treatment with chemotherapy or radiation therapy.

Common complications of cytotoxic (cell-killing) systemic chemotherapy include immunosuppression and mucositis (ulcers of mucosal surfaces often with bacterial or fungal superinfection). Complications of radiation therapy occur as acute and/or chronic side effects. Acute side effects include damage to epithelial surfaces with ulceration and skin breakdown. Chronic side effects include fibrosis and diffuse scarring, which also affects the circulatory

[752] ETH-02955: Deffieux X et al. Vaginal mesh erosion after transvaginal repair of cystocele using Gynemesh or Gynemesh-Soft in 138 women: a comparative study. Int Urogynecol J 2007 Jan; 18: (1): 73-79. Epub 2006 Jan 4.
[753] http://www.cancer.org/Cancer/CancerBasics/lifetime-probability-of-developing-or-dying-from-cancer

system to diminish blood flow to areas that have received radiation. If the bone marrow receives radiation either intentionally or as a side effect, immunosuppression can occur. Some experts believe that immunosuppression and previous radiation therapy are relative contraindications to the placement of a synthetic permanent mesh implant.[754] Considering the combination of systemic and local effects from chemotherapy and radiotherapy, it seems extremely likely that mesh-related complications will occur in women who have had previous Prolift mesh implantation, including vaginal mesh exposure and mesh infection that would likely require mesh excision. If complete mesh excision was necessary, that procedure would carry a high risk of significant morbidity, given the tissue changes associated with chemotherapy and/or radiation therapy, in addition to chronic changes of inflammation and foreign body reaction due to the Prolift mesh. After complete mesh excision, prolapse could recur, and reoperation for recurrent prolapse would also carry a high risk of morbidity. Ethicon never warned physicians or patients of these risks associated with permanent Prolift mesh implantation.

Diabetes is another example of a very frequently occurring condition that may increase the lifetime risk of Prolift mesh-related complications. Women have an approximately 2 in 5 chance (40%) of developing diabetes in their lifetime.[755] In 2011, 27% of people aged 65 years and over had diabetes, representing 10.9 million people.[756] The percentage of people diagnosed with diabetes has increased by a factor of more than 7-fold between 1958 and 2010, in part due to the obesity epidemic.[757] In women aged 60 years and older, 42.3% are obese.[758] Some experts believe that poorly controlled diabetes and perhaps morbid obesity are relative contraindications for synthetic permanent mesh implantation.[759] People with diabetes are well known to be at increased risk for infection and to have impaired wound healing.[760] Although not yet studied, this seems likely to apply to infection after permanent Prolift mesh implantation and to vaginal wound healing and wound maintenance overlying Prolift mesh implantation. Ethicon has never studied what will happen in women after Prolift mesh implantation when diabetes is a current comorbidity and certainly not as a future factor in vaginal wound healing, breakdown, infection, or other Prolift mesh-related complications. Ethicon never warned physicians and patients of the possibility of increased risk of Prolift mesh-related complications in women with diabetes.

Another problem of increasing concern is interference of the Prolift mesh and its surrounding inflammatory tissue reaction with the proper interpretation of radiologic imaging

[754] ETH.MESH.00164458: Davila GW et al. Clinical implications of the biology of grafts: conclusions of the 2005 IUGA Grafts Roundtable. Int Urogynecol J 2006; 17: S51-S55.
[755] http://www.cdc.gov/diabetes/news/docs/lifetime.htm
[756] Centers for Disease Control and Prevention. National diabetes fact sheet: national estimates and general information on diabetes and prediabetes in the United States, 2011. Atlanta, GA: U.S. Department of Health and Human Services, Centers for Disease Control and Prevention, 2011.
[757] http://www.cdc.gov/diabetes/statistics/slides/long_term_trends.pdf
[758] Ogden CL, Carroll MD, Kit BK, Flegal KM. Prevalence of obesity in the United States, 2009–2010. NCHS data brief, no 82. Hyattsville, MD: National Center for Health Statistics. 2012.
[759] ETH.MESH.00164458: Davila GW et al. Clinical implications of the biology of grafts: conclusions of the 2005 IUGA Grafts Roundtable. Int Urogynecol J 2006; 17: S51-S55.
[760] Wu SC et al. Wound care: the role of advanced wound healing technologies. J Vasc Surg 2010; 52 (3 Suppl): 59S-66S.

studies. In patients with remote Prolift mesh implantation or in patients who don't know or don't remember that they have had Prolift mesh implantation, it seems very likely that abnormal radiologic findings will prompt further aggressive testing to reach a diagnosis to explain the findings or at least to rule out dangerous diagnoses such as invasive cancer.

In addition, presence of the Prolift mesh and its surrounding reaction creates radiologic findings that obscure the differential diagnosis of hematoma versus abscess, a critically important distinction in determining appropriate management.[761] Another example of confusing radiologic findings with important clinical implications was described in a summary of Prolift complaints. A patient had postoperative spotting, granulation tissue was treated, and "more induration than usual" was noted at the vaginal cuff. Findings on CT scan included "air bubbles around the graft," and at least one radiologist questioned whether a surgical sponge was left behind at the time of surgery.[762] No further information on evaluation or treatment was given.

Complications such as abscesses can be mistaken for soft tissue cancers such as sarcoma,[763] and radiologic findings are not necessarily helpful in clarifying the diagnosis, thereby necessitating risky and invasive testing that may cause additional morbidity due to the Prolift mesh implant. For example, needle biopsies of suspicious areas are often performed under radiologic guidance to reach otherwise inaccessible tissues. Since the biopsy needle must traverse the skin to reach deeper tissues, the introduction of skin bacteria is inevitable, even with standard antiseptic skin preparation. Normally, the body is capable of clearing the relatively small burden of bacteria introduced in such a way. However, if the biopsy needle traverses the Prolift mesh implant, that may trigger a full-blown infection of the Prolift mesh-implanted area and require medical and/or surgical treatment. Obviously, this is not a risk that follows traditional vaginal prolapse surgery. Nor is it a risk that Ethicon warned physicians and patients of.

It is of great concern to contemplate the number of women around the world who have had the Prolift procedure and permanent Prolift mesh implantation, as they begin to age and develop new medical problems unrelated to prolapse. The evaluation and treatment of these new medical problems will be unreasonably complicated by the presence of the permanent Prolift mesh implant and will lead to new Prolift mesh-related complications that will cause symptoms and require treatment. Already, surgeons who are experienced in removing transvaginal mesh implants describe the creation of a "subspecialty" dedicated to managing the growing number of mesh-related complications. This will be a public health crisis that could easily overwhelm the relatively small number of surgeons who are qualified to care for patients with such complex complications. An epidemic of Prolift mesh-related complications is already occurring and will only worsen with time. Truly, this is a "ticking time bomb" to which Ethicon gave absolutely no

[761] ETH.MESH.02645424
[762] ETH.MESH.03647181
[763] Yeung P Jr et al. Thigh abscess mistaken for sarcoma following transobturator tape: a case report and literature review. J Minim Invasive Gynecol 2007; 14: 657-659.

consideration in its rush to market with the Prolift product and its aggressive marketing of the Prolift procedure as appropriate for "almost all patients."

XII. The 2010 Prolift Clinical Expert Report, 7-2-2010[764]

A. Manufacturer's Statement on the Clinical Data Used to Affix CE-Mark

"The following clinical evaluation is based on the assessment of the risks and the benefits, associated with the use of the device through:

- ✓ A compilation of relevant scientific literature that is currently available, as well as a written report containing a critical evaluation of this compilation."

B. Device Description & Background[765]

Indications statement; set of components in each kit; sterilization; description of Gynemesh PS mesh and Prolift implants and inserter tools; reaction of Gynemesh PS mesh to implantation; statement regarding safety and effectiveness from Prolift IFU.

"Randomized, controlled clinical evaluations of the Gynecare Prolift System are underway. In 2008, data was [sic] published from two early observational studies of transvaginal mesh that were initiated in 2004. These observational studies evaluated a pre-cut surgical mesh made of the same non-absorbable polypropylene as the mesh used in the Gynecare Prolift System. For these studies, the mesh was provided in a shape similar to that of the Gynecare Prolift System, although implantation instruments were not provided in these studies. …"

Analysis

1) Ethicon has never provided any evidence that randomized, controlled clinical evaluations of the Prolift kit were underway at the time this statement was added to the Prolift IFU after FDA review in 2008,[766] or since then.

2) The statements regarding the observational studies apparently refer to the Ethicon French and US TVM studies. However, results of the TVM studies were not published in 2008.

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[764] ETH.MESH.00306701

[765] See Prolift IFU for a detailed discussion of false and misleading statements referring to Gynemesh PS mesh in the Prolift IFU.

[766] However, the revised Prolift IFU was not actually available until nearly 1-½ years after FDA clearance. ETH.MESH.02341734

Abstracts were presented in 2005[767] and 2006,[768] and articles were published in 2010[769] and 2011.[770] Nevertheless, these presentations and publications did not disclose the true frequency of complications, especially the very high reoperation rate, with the TVM procedure. (See Medical Literature Review for a detailed discussion of the TVM studies.)

Device Description & Background, continued

Contraindications, Warnings, Precautions, Adverse Reactions, Disposal, Storage; no changes in mesh, two changes in packaging materials, several changes to package labeling and IFU labeling.

Analysis

Ethicon failed to note how many changes and additions to labeling, including the Prolift IFU and patient brochure, were required due to FDA review. In fact, Ethicon failed to even mention the fact that FDA clearance of Prolift through the 510(k) process was only obtained in May 2008.[771]

C. Literature Review

Introduction

… Specifically, this review produced a safety analysis of synthetic mesh grafts used in vaginal urogenital prolapse repair techniques.

The primary objective of the review was to provide the most current, documented clinical experience as insight into the following:

- The scientific background of tissue changes and wound healing in prolapse patients

Analysis

[767] ETH.MESH.00482987: Miller D et al. Trans-Vaginal Mesh (TVM): An Innovative Approach to Placing Synthetic Mesh Transvaginally for Surgical Correction of Pelvic Support Defects – Peri-operative Safety Results. ICS/IUGA Abstract 406, August 2005.

[768] ETH-02276: Cosson M et al. Prospective clinical assessment of the total vaginal mesh (TVM) technique for treatment of pelvic organ prolapse - 6 and 12 month results. IUGA 2006.

[769] ETH.MESH.01205254: Jacquetin B et al. Total transvaginal mesh (TVM) technique for treatment of pelvic organ prolapse: a 3-year prospective follow-up study. Int Urogynecol J 2010; 21:1455-1462. Epub Aug 4 2010.

[770] Miller D et al. Prospective clinical assessment of the transvaginal mesh technique for treatment of pelvic organ prolapse – 5 year results. Female Pelvic Med Reconstr Surg 2011; 17: 139-143.

[771] ETH-01363

In terms of "tissue changes," Ethicon ignored the accumulation of evidence in the medical literature, spanning decades, that the inflammatory reaction elicited by polypropylene mesh is NOT transient and minimal, and polypropylene is NOT inert, as Ethicon claimed in the IFUs for Gynemesh PS mesh and Prolift.[772] The inflammatory reaction elicited by polypropylene mesh is chronic, indeed lifelong,[773] and the reaction is severe in some individuals described as "high responders."[774] Polypropylene degrades over time, particularly in a setting of chronic inflammation that polypropylene itself incites.[775] If Ethicon were truly committed first and foremost to patient safety, Ethicon would not have ignored these compelling findings in the literature and would have appropriately studied and tested this known phenomenon to determine whether the product could be safety manufactured given the nature of this design characteristic and if so, corrected all the IFUs for its mesh products that included these false claims.

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[772] Gynemesh PS mesh IFUs: ETH.MESH.02342194; ETH.MESH.02342278; ETH.MESH.02342218; ETH.MESH.02342250
Prolift IFUs: ETH.MESH.02341522; ETH.MESH.02341454; ETH.MESH.02341734; ETH.MESH.02341658

[773] Chronic inflammatory foreign body reaction at the mesh interface. Klinge U et al. Impact of polymer pore size on the interface scar formation in a rat model. J Surg Res 2002; 103: 208-214. Epub March 6, 2002. ETH-60811
"… PP [polypropylene] … moderate chronic inflammation of the foreign body type with an intense fibrosis. …" Klosterhalfen B et al. The lightweight and large porous mesh concept for hernia repair. Expert Rev Med Devices 2005 Jan; 2: 103-117. ETH-60818
"… macroscopical appearance of explanted meshes being shrunk, folded and rolled and the histological evidence of persistent inflammation over a period of years. Altogether indicate that meshes are not always inertly incorporated. …" "… [fistulas] may develop after 3 months or 15 years." Klinge U, Klosterhalfen B. Chapter 15: Biomaterials - experimental aspects. ETH-77160

[774] Schachtrupp A et al. Individual inflammatory response of human blood monocytes to mesh biomaterials. Br J Surg 2003; 90: 114-120. Epub 12-12-2002.

[775] Liebert TC et al. Subcutaneous implants of polypropylene filaments. J Biomed Mater Res 1976 Nov; 10(6): 939-951. Degradation begins to occur after only a few days, possibly by the mechanism of auto-oxidation.
Postlethwait RW. Five year study of tissue reaction to synthetic sutures. Ann Surg 1979; 190: 54-57. Sutures implanted in abdominal walls of rabbits and sampled from 6 months to 5 years. Polypropylene sutures showed fragmentation in 4% and perisutural formation of bone, cartilage, or both in 2.6%.
Tuberbille AW et al. Complement activation by nylon- and polypropylene-looped prosthetic intraocular lenses. Invest Ophthalmol Vis Sci 1982; 22: 727-733. Polypropylene activated complement release that mediates acute inflammatory reactions.
Jongeboed WL, Worst JF. Degradation of polypropylene in the human eye: a SEM study. Doc Ophthalmol 1986; 64: 143-152. Polypropylene suture removed after 6.5 years and compared to unused suture. Findings: cracks perpendicular to the longitudinal axis of the suture, part of the surface layer was nearly detached or completely missing; diameter of suture was decreased toward both ends by over 50%; exposed subsurface area layer showed a fibrillar structure. Degradation considered to be caused by the enzymatic action of tissue fluids.
"Oxidation would result in surface cracking, decreased melting temperature, loss of mass, and reduced compliance of the material. … the results supported our hypothesis that oxidation is involved with the degradation of polypropylene hernia mesh materials." Costello CR et al. Materials characterization of explanted polypropylene hernia meshes. J Biomed Mater Res B Appl Biomater 2007; 83 (1): 44-49.
Clave A et al. Polypropylene as a reinforcement in pelvic surgery is not inert: comparative analysis of 100 explants. Int Urogynecol J March 2010; 21:261-270. Epub 2010 Jan 6. PLTMEDLIT01605

Literature Review, Introduction, continued

- Issues or concerns regarding the use of the implant materials used to reinforce repairs to include: infection, seroma formation, shrinkage, erosion and fistula formation

Analysis

1) Although Ethicon claimed that the literature review in this report would include the issue of infection in regard to the use of implant materials, astonishingly, infection is not even included in the following list of specific complications that the literature review was intended to summarize. Considering that infection has always been one of the issues of greatest concern, given that permanent Prolift mesh implantation occurs in the clean-contaminated surgical environment of the vagina, how Ethicon could manage to omit the complication of infection from its review is inexplicable.

2) From the hernia literature, Ethicon already knew the risks and clinical consequences of polypropylene mesh "shrinkage" or contraction/retraction. As transvaginal mesh use increased, articles in the medical literature (available at the time of this Clinical Expert Report) reported similar findings of substantial mesh shrinkage and clinical consequences of pelvic pain, vaginal pain, dyspareunia, and recurrent prolapse.[776,777,778,779] Ethicon ignored this accumulating body of evidence, despite its stated claim that the "primary objective of the review was to provide the most current, documented clinical experience as insight into" exactly these issues.

Literature Review, Introduction, continued

- Recommended standards of care from well-regarded sources to include: Status of any Cochrane reviews or similar critical examinations of the literature regarding synthetic mesh use

Analysis

[776] PLTMEDLIT-01252 (cited in ETH-02326): Tunn R, Picot A, Marschke J, Gauruder-Burmester A. Sonomorphological evaluation of polypropylene mesh implants after vaginal mesh repair in women with cystocele or rectocele. Ultrasound Obstet Gynecol 2007; 29: 449-452. Epub 1 March 2007.
[777] PLTMEDLIT-01247 (cited in ETH-02314): Shek KL, Dietz HP, Rane A, Balakrishnan S. Transobturator mesh for cystocele repair: a short- to medium-term follow-up using 3D/4D ultrasound. Ultrasound Obstet Gynecol 2008; 32: 82-86. Epub 10 June 2008.
[778] PLTMEDLIT-01252 (cited in ETH-02326): Tunn R, Picot A, Marschke J, Gauruder-Burmester A. Sonomorphological evaluation of polypropylene mesh implants after vaginal mesh repair in women with cystocele or rectocele. Ultrasound Obstet Gynecol 2007; 29: 449-452. Epub 1 March 2007.
[779] Velemir L et al. Transvaginal mesh repair of anterior and posterior vaginal wall prolapse: a clinical and ultrasonographic study. Ultrasound Obstet Gynecol 2010 Apr; 35: 474-480.

Consistent with Ethicon's practice of selective reporting, even from "well regarded sources," Ethicon failed to include any information from authoritative compendiums such as the International Consultation on Incontinence, published by the International Continence Society. In the 2005 Third International Consultation on Incontinence (which, despite the title, covers all aspects of pelvic floor disorders), the chapter on prolapse surgery had several strongly-worded, negative conclusions about transvaginal mesh use in prolapse surgery.[780] The prolapse surgery chapter in the updated 2009 fourth edition describes mesh-based procedures as posing "known serious risks," causing "concern," and due to the "uncertainty of long-term functional outcomes," requiring further evaluation to determine the risk/benefit ratio, particularly regarding mesh implantation for primary prolapse procedures.[781] The 2009 chapter stated that "There is insufficient information to provide evidence-based recommendations for the optimal vaginal repair approach, including technique and materials" and enumerated several types of study results that needed to be performed for mesh-based procedures. Despite the comprehensive nature of these chapters (156 references in the third edition and 323 references in the fourth edition), Ethicon ignored the wealth of this evidence and included none of it in the Prolift Clinical Expert Report.

Literature Review, Introduction, continued

[780] PLTMEDLIT00724: Abrams P et al. Third International Consultation on Incontinence. Edition 2005. Brubaker L et al. Surgery for pelvic organ prolapse. Chapter 21.
Summary of Evidence: "Transvaginal placement of permanent mesh may reduce anterior wall recurrent [sic] but has an unacceptable high rate of complications that include erosion, infection, sepsis, dyspareunia and other functional symptoms." "There is no evidence to support the routine use of biological or permanent synthetic grafts for transvaginal POP repair."
Research Recommendations: "Transvaginal permanent grafts for prolapse repair have a poor risk/benefit ratio, therefore use of these materials should only occur in approved clinical trials."

[781] Abrams P et al. Fourth International Consultation on Incontinence. Edition 2009. Brubaker L et al. Surgery for pelvic organ prolapse. Committee 15.
Recommendations: "There is insufficient information to provide evidence-based recommendations for the optimal vaginal repair approach, including technique and materials."
"The emergence of mesh-based procedures poses a dilemma as there is significant uncertainty about the safety and efficacy of secondary prolapse procedures for prolapse recurrence following a primary mesh procedure. There are surgical concerns regarding the status of normal dissection planes, especially following a uterine-conserving mesh-based procedure. Given the high success rates of sacrocolpopexy in women with recurrent prolapse, the risk/benefit ratio of routine mesh placement for primary prolapse procedures needs further evaluation. Appropriate counseling of patients must include the known serious risks of mesh placement and the uncertainty of long-term functional outcomes."
"Well-designed RCT studies are needed to [bulleted list] … compare native tissue vs. mesh-based apical repair techniques; … determine the optimal technique for repair of recurrence after primary mesh repair in any compartment. Well-designed comparative studies are needed to study [bulleted list] the utility of self-prepared mesh vs. kit-prepared mesh for apical and/or anterior prolapse repairs; the safety and efficacy of prolapse-repair meshes that include arms that non-vaginal spaced; management of complications especially mesh contracture and complications associated with armed meshes; and management of recurrent anterior compartment prolapse following unsuccessful permanent mesh."

Search Strategy from 2000-2009, Search Databases and Summary Findings

Summary of search results:
- 194 IUGA abstracts 2001 to 2008
- 44 IUGA 2009 abstracts
- 10 relative [sic] articles (safety and complication rates) PubMed (2000 to 2009)
- 1 Cochrane Database of Systematic Reviews review
- 6 National Institute for Health and Clinical Excellence Guidance documents

Selection Criteria

"… Substantially based on the compilation of data from the IUGA congress reports, versus PubMed cited literature entirely, in order to capture as many patients as possible through the combination of all smaller series reported through the series of IUGA congresses, known to focus on these types of procedures more than any other international body or association."

Analysis

1) The above summary of the search results indicates that Ethicon located a total of 10 articles reporting safety and complication rates from PubMed from 2000 to 2009. That Ethicon claims that this represents "a compilation of relevant scientific literature that is currently available," as stated at the very beginning of this report, would be laughable if not for the very serious nature of the subject matter. This raises the suspicion that Ethicon carefully selected certain articles as being favorable or least damaging, in order to be able to conclude that the safety and performance of the Prolift Systems had been demonstrated.

2) Apparently, Ethicon relied most heavily on IUGA abstracts representing non-peer-reviewed data over published literature. Ethicon provided a very weak rationale for relying on abstracts, "in order to capture as many patients as possible through the combination of all smaller series reported through the series of IUGA congresses, known to focus on these types of procedures more than any other international body or association." Reliance by Ethicon on abstracts alone, and particularly those abstracts that are not followed by publication in peer-reviewed literature, is inadequate because the data they represent are not as reliable or the results of the well-designed, well-implemented studies that would typically be published in the medical literature. It is well recognized in the scientific community that the content and even the conclusion of abstracts can change between submission and presentation, often based on the addition of data collected between submission and presentation. Furthermore, in this report, Ethicon did not cite particular abstracts, so there is no way to independently evaluate the quality of the data cited. Ethicon's choice to inordinately rely on abstracts over peer-reviewed published literature apparently suited Ethicon's purpose.

3) Ethicon presented no rationale for choosing the abstracts presented at only one meeting, IUGA, over other international or national professional meetings that focus on pelvic floor disorders, such as the International Continence Society, the American Urogynecologic

Society, or the Society of Gynecologic Surgeons. Moreover, Ethicon presented no rationale for failing to summarize all available abstracts and excluding those abstracts presented at other international and national professional meetings that focus on pelvic floor disorders.

Literature Review, continued

Findings for Synthetic Mesh Grafts Used in Vaginal Urogenital Prolapse Repair

a. Overall Findings

The overall success rates for anterior vaginal wall prolapse surgery using synthetic grafts is higher than when performing traditional techniques with gross success in more than 86% compared to 72% respectively after a variable but short-term follow up. Mean reported erosion rates using synthetic grafts in the anterior compartment range from 2.6% - 6.8% and from 0 to 12.1% and from 4.7 to 14.4% in the posterior and middle compartment respectively. Other complications are rare, with the most frequently reported being bladder perforations ranging from a mean of 1.8% to 3.8% of cases in studies reporting upon this complication.

Analysis

1) Ethicon failed to provide any citations to support its "overall findings."

2) Ethicon failed to disclose that "better" anatomic outcomes of mesh-based anterior vaginal prolapse repair are not accompanied by any difference in subjective improvement or improved quality of life, when mesh-based repairs are compared with traditional vaginal prolapse surgery.

3) Ethicon claimed mesh erosion occurred at most in 6.8% of patients after mesh-based anterior vaginal prolapse repair, yet the 2010 Cochrane review reported mesh erosion in 10% of patients after anterior repairs with polypropylene mesh.[782]

4) Furthermore, Ethicon claimed that "other" complications, besides mesh erosion, were "rare." Obviously, bladder perforations at a frequency of 1.8% to 3.8% are NOT rare. Ethicon does not name other complications that occur after transvaginal mesh surgery, particularly trocar-based surgery like the Prolift procedure. The claim that other complications are rare is also contradicted by evidence in the medical literature; one systematic review found that of complications after mesh kits, 14.5%, most required surgical intervention under general anesthesia, in contrast to complications after traditional vaginal prolapse surgery and sacral

[782] Maher C et al. Surgical management of pelvic organ prolapse in women. Cochrane Database Syst Rev 2010 Apr 14; (4): CD004014.

colpopexy, in which most complications needed no intervention or pharmacologic intervention.[783]

Literature Review, continued

b. General Conclusion:

Scientific evidence demonstrating a low recurrence rate of prolapse after novel needle suspension techniques with mesh is accumulating. This improved outcome compared to traditional repairs to treat urogenital prolapse is partially offset by an additional morbidity related to the use of mesh grafts. This is almost solely related to mesh erosion. Chronic or life threatening complications are considered rare. Hemorrhagic incidences and de novo dyspareunia appear to be less than in techniques involving traditional vaginal repairs or abdominal sacrocolpopexies.

Analysis

1) Ethicon failed to provide any citations for its "General Conclusion."

2) Despite Ethicon's claim to the contrary, improved outcomes from the patient's point of view have NOT been demonstrated for mesh-based repair.

3) Ethicon claimed that "improved outcome" after transvaginal mesh surgery is "partially offset by an additional morbidity related to the use of mesh grafts." This claim is contradicted by evidence in the medical literature, including a systematic review that found that most complications after mesh kits require surgical intervention under general anesthesia (Dindo grade IIIb).[784] In addition, this review found that mesh kits had the highest reoperation rate (8.5%) compared with traditional vaginal prolapse surgery (5.8%) and sacral colpopexy (7.1%), despite mesh kits having the shortest follow-up (mean 17 months) compared with traditional vaginal prolapse surgery (33 months) and sacral colpopexy (26.5 months). The higher reoperation rate alone would more than offset the inaccurately claimed "improved outcome" after transvaginal mesh surgery, which does not even consider all the other morbidity related to the use of mesh grafts.

4) Moreover, additional morbidity from transvaginal mesh surgery is emphatically NOT "almost solely related" to mesh erosion. Trocar-based transvaginal mesh surgery, including the Prolift procedure, introduces an entirely new category of complications from blind passage of

[783] PLTMEDLIT00139: Diwadkar GB, Barber MD, Feiner B, Maher C, Jelovsek JE. Complication and reoperation rates after apical vaginal prolapse surgical repair: a systematic review. Obstet Gynecol 2009 Feb; 113: 367-373.
[784] PLTMEDLIT00139: Diwadkar GB, Barber MD, Feiner B, Maher C, Jelovsek JE. Complication and reoperation rates after apical vaginal prolapse surgical repair: a systematic review. Obstet Gynecol 2009 Feb; 113: 367-373.

several trocars through deep pelvic tissues and a new category of complications involving non-vaginal, non-pelvic tissues because of Prolift mesh implantation through otherwise normal structures in the hip and thigh. In addition, mesh-related complications are not restricted to mesh exposure but include mesh retraction (and its associated complications of mesh exposure and recurrent prolapse), visceral mesh erosion, and the accompanying symptoms of pelvic pain, vaginal pain, and dyspareunia, to name a few.

5) Without citing any evidence, Ethicon claimed that chronic and life-threatening complications are "rare." Chronic complications are NOT rare, given the chronic inflammatory and foreign body reaction caused by permanent implantation of Prolift mesh, that in turn causes persistent and recurrent complications and symptoms that can be refractory even to the most aggressive treatments, resulting in permanent symptoms and disabilities that are essentially untreatable. Ethicon did not disclose any information related to the LIFE-LONG risk of mesh-related complications that occur in women even years after the index Prolift surgery. Ethicon did not disclose the difficulty, if not the impossibility, of completely removing the Prolift mesh implant when required by the severity and persistence of symptoms and complications; in addition, Ethicon did not disclose the additional morbidity incurred by women who require multiple operations in an attempt to completely remove the permanent Prolift mesh implant. Moreover, Ethicon did not disclose the morbidity of permanent Prolift mesh implantation in non-vaginal, non-pelvic structures that had no involvement in the prolapsed area.

6) With no citation to evidence, Ethicon claimed that "hemorrhagic incidences" and "de novo dyspareunia" are less frequent after transvaginal mesh surgery than traditional vaginal prolapse surgery and sacral colpopexy. The Cochrane review reported that blood loss with transobturator meshes was significantly higher than for native tissue anterior repair.[785] In Diwadkar's systematic review, the weighted average for dyspareunia was highest after mesh kits compared with traditional vaginal prolapse surgery and sacral colpopexy.[786]

Literature Review, continued

c. Detailed Findings

- There are an increasing number of reviews in the literature suggesting that the insertion of a prosthetic mesh in a tension-free fashion via the vagina in patients suffering from symptomatic urogenital prolapse will reduce the chance of recurrence in certain indications. [Jia, Feiner, Sung, De Ridder]

- Similarly, the Maher et al study first published within the Cochrane Database of Systematic Reviews in October 2004 and recently updated, April 2010, concluded: "the use of

[785] Maher C et al. Surgical management of pelvic organ prolapse in women. Cochrane Database Syst Rev 2010 Apr 14; (4): CD004014.
[786] PLTMEDLIT00139: Diwadkar GB, Barber MD, Feiner B, Maher C, Jelovsek JE. Complication and reoperation rates after apical vaginal prolapse surgical repair: a systematic review. Obstet Gynecol 2009 Feb; 113: 367-373.

mesh or graft inlays at the time of anterior vaginal wall repair reduces the risk of recurrent anterior wall prolapse, on examination. …"

Analysis

1) In its claim regarding "urogenital prolapse," Ethicon made no distinction between the types of prolapse, implying that graft insertion has been proven beneficial for all types of prolapse, when this is not the case.

2) Moreover, Ethicon did not name the "certain indications" for which mesh implantation reduced recurrent prolapse.

3) Ethicon cited 4 review articles to support its claim that mesh implantation reduces recurrent prolapse. Of these 4 reviews, only 1 comparative study showed a benefit for any type of mesh implantation, restricted to anterior vaginal prolapse, with insufficient information to compare any of the other outcomes regardless of prolapse type.[787] The only other comparative article concluded that "Data in the current literature are insufficient to allow for a complete assessment of anatomic or symptomatic efficacy of graft use in transvaginal POP repair for any compartment."[788] The other 2 reviews were not comparative.[789]

Furthermore, all of these reviews commented on the paucity of data, particularly on outcomes of importance to women,[790] and cautioned that it was premature to accept widespread mesh use before long-term data, especially related to the life-long risk of mesh-related complications, were available.[791,792,793,794] In fact, one author stated that "It would be

[787] PLTMEDLIT00154: Jia X et al. Efficacy and safety of using mesh or grafts in surgery for anterior and/or posterior vaginal wall prolapse: systematic review and meta-analysis. BJOG 2008; 115: 1350-1361. Epub August 19, 2008.
[788] PLTMEDLIT00174: Sung VW et al. Graft use in transvaginal pelvic organ prolapse repair: a systematic review. Obstet Gynecol November 2008; 112: 1131-1142.
[789] PLTMEDLIT00068: Feiner B, Jelovsek JE, Maher C. Efficacy and safety of transvaginal mesh kits in the treatment of prolapse of the vaginal apex: a systematic review. BJOG 2009; 116: 15-24.
PLTMEDLIT01209: De Ridder D. Should we use meshes in the management of vaginal prolapse? Curr Opin Urol 2008; 18: 377-382.
[790] PLTMEDLIT00154: Jia X et al. Efficacy and safety of using mesh or grafts in surgery for anterior and/or posterior vaginal wall prolapse: systematic review and meta-analysis. BJOG 2008; 115: 1350-1361. Epub August 19, 2008. "It is increasingly recognized that in prolapse surgery, subjective failure is a more appropriate outcome measure of efficacy than objective failure."
[791] PLTMEDLIT00068: Feiner B, Jelovsek JE, Maher C. Efficacy and safety of transvaginal mesh kits in the treatment of prolapse of the vaginal apex: a systematic review. BJOG 2009; 116: 15-24. "Surgeons should counsel women that device-related complications that may occur when using these procedures are not rare; most are related to the use of mesh and their management might necessitate surgical intervention under an anaesthetic."
[792] PLTMEDLIT01209: De Ridder D. Should we use meshes in the management of vaginal prolapse? Curr Opin Urol 2008; 18: 377-382. "Long-term controlled studies will have to confirm the effectiveness and safety of new mesh and will have to include more functional data on sexuality and quality of life, before transvaginal meshes can be accepted as routine surgery."

irresponsible, however, to start using vaginal meshes that have not yet undergone any considerable clinical testing outside of some form of a clinical trial."[795] Responsible surgeons would be appalled to learn that this is exactly what Ethicon did, aggressively marketing the Prolift procedure before "any considerable clinical testing" had been done, indeed, before any clinical testing at all. Instead, unsuspecting women underwent this "clinical testing," without their explicit knowledge or consent that they were acting as research subjects under the guise of clinical care.

4) In citing the Maher et al Cochrane review, Ethicon only included wording that suited its purposes and failed to include other conclusions drawn by the authors of the Cochrane review:

- "Evidence of benefit to the woman, including symptoms and quality of life improvement, is lacking for use of grafts over native tissue repairs."[796]
- "No data exist on efficacy or otherwise of polypropylene mesh in the posterior vaginal compartment."[797]

Literature Review, (c) Detailed Findings, continued

- Looking at the global success rates of graft reinforced vaginal prolapse procedures, there was noted a higher success rate when compared to traditional repairs. For the two mesh kits most reported upon, the mean success rates were 93 and 87% respectively, after a short mean follow up time of 8 and 6 months. For both procedures a range of successes between 80 and 100% could be found; traditional repairs, reported upon in the traditional repair arms of comparative studies, on the contrary, only reported success rates between 62 and 88%, with a mean of 74%. It must be noted that the follow up time for this group of patients was significantly longer, however, at a mean of 18 months.

Analysis

1) Ethicon provided no citations for the results in this paragraph, making it impossible to assess the sources of these data.

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[793] PLTMEDLIT00174: Sung VW et al. Graft use in transvaginal pelvic organ prolapse repair: a systematic review. Obstet Gynecol November 2008; 112: 1131-1142. "Adequately powered randomized trials evaluating anatomic and symptomatic efficacy as well as adverse events are needed."

[794] PLTMEDLIT00154: Jia X et al. Efficacy and safety of using mesh or grafts in surgery for anterior and/or posterior vaginal wall prolapse: systematic review and meta-analysis. BJOG 2008; 115: 1350-1361. Epub August 19, 2008. "Rigorous long-term RCTs are required to determine the comparative efficacy of using mesh/graft."

[795] PLTMEDLIT01209: De Ridder D. Should we use meshes in the management of vaginal prolapse? Curr Opin Urol 2008; 18: 377-382.

[796] PLTMEDLIT00905: Maher C et al. Surgical management of pelvic organ prolapse in women: Cochrane review. 2010, issue 8. Plain language summary.

[797] Maher C et al. Surgical management of pelvic organ prolapse in women. Cochrane Database Syst Rev 2010 Apr 14; (4): CD004014.

2) Again, Ethicon focused exclusively on anatomic outcomes without regard for outcomes of importance to patients, despite the growing conviction among clinician-scientists that quality of life and patient-oriented outcomes should be considered as the primary outcome for treatment of prolapse, a condition that impairs quality of life.[798]

3) Ethicon acknowledged the important difference in length of follow-up in comparisons between mesh kits and traditional prolapse surgery. However, Ethicon did not disclose that available studies of transvaginal mesh surgery with longer follow-up have shown considerable deterioration in anatomic outcomes over time.[799]

Literature Review, (c) Detailed Findings, continued

- The emergence of a new morbidity accompanying the commercialization of mesh repair kits for urogenital prolapse has stirred a lively debate between mesh adopters and antagonists. [Nygaard, IJUG 2007, Isom-Batz G, Exp Rev Med Dev 2007, Swift, IJUG 2007, Paraiso JMIG 2008]

Analysis

1) Ethicon acknowledged the "emergence of a new morbidity" of transvaginal mesh kits, yet continued to claim that complications were "rare."

2) Ethicon described a "lively debate" as if this were a purely intellectual exercise, as opposed to grave concern among clinicians that patients were being harmed far out of proportion to any "benefit" obtained by the Prolift procedure. If Ethicon had patient safety as its highest priority, Ethicon would also be gravely concerned about patient harm.

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[798] Barber MD et al. Defining success after surgery for pelvic organ prolapse. Obstet Gynecol 2009; 114: 600-609.
PLTMEDLIT00154: Jia X et al. Efficacy and safety of using mesh or grafts in surgery for anterior and/or posterior vaginal wall prolapse: systematic review and meta-analysis. BJOG 2008; 115: 1350-1361. Epub August 19, 2008.
"It is increasingly recognized that in prolapse surgery, subjective failure is a more appropriate outcome measure of efficacy than objective failure."

[799] ETH-60188: Hiltunen R et al. Low-weight polypropylene mesh for anterior vaginal wall prolapse: a randomized controlled trial. Obstet Gynecol 2007; 110 (2 Pt 2): 455-462.
ETH-76654: Nieminen K et al. Symptom resolution and sexual function after anterior vaginal wall repair with or without polypropylene mesh. Int Urogynecol J 2008; 19: 1611-1616. Epub 21 Aug 2008.
PLTMEDLIT01406: Nieminen K et al. Outcomes after anterior vaginal wall repair with mesh: a randomized controlled trial with a 3 year follow-up. Am J Obstet Gynecol 2010 (3): 235.e1-8. Epub 2010 May 21.
ETH.MESH.01205254: Jacquetin B et al. Total transvaginal mesh (TVM) technique for treatment of pelvic organ prolapse: a 3-year prospective follow-up study. Int Urogynecol J 2010; 21:1455-1462. Epub Aug 4 2010. Although this study was not published until August 4, 2010, and the Prolift Clinical Expert Report was completed on July 2, 2010, Ethicon surely had access to the data and the manuscript before publication, since the study reported on the French TVM study cohort.

3) Ethicon dismissed these concerned clinicians as mesh "antagonists," versus Ethicon's customers, "mesh adopters," once again revealing that Ethicon held its commercial concerns as its highest priority, rather than patient safety, in direct contradiction of the Johnson & Johnson credo.

Literature Review, (c) Detailed Findings, continued

- On October 20, 2008, the United States Food and Drug Administration (FDA) issued a Public Health Notification entitled "Serious Complications Associated with Transvaginal Placement of Surgical Mesh in Repair of Pelvic Organ Prolapse and Stress Urinary Incontinence." Over three years, the FDA had received over 1,000 reports from nine surgical mesh manufacturers of complications that were associated with surgical mesh devices used to repair pelvic organ prolapse and stress urinary incontinence. They stated in their notification that "although rare, these complications can have serious consequences."

Analysis

1) The FDA listed the most frequent complications of transvaginal mesh surgery. In this Clinical Expert Report, Ethicon failed to address certain complications, including infection, urinary problems, and recurrent prolapse. This is yet another example of Ethicon attempting to minimize reporting of complications due to the Prolift product and procedure, ultimately, to support its conclusion that Prolift is safe enough to continue marketing.

2) Ethicon ignored other findings of the FDA in their Public Health Communication, including that "vaginal scarring and mesh erosion led to a significant decrease in patient quality of life due to discomfort and pain, including dyspareunia."

3) In its listing of complications due to the Prolift product and procedure, Ethicon failed to include the morbidity of subsequent treatment, as stated by the FDA, that included "additional surgical procedures (some of them to remove the mesh), IV [intravenous] therapy, blood transfusions, and drainage of hematomas or abscesses."

4) Ethicon ignored the FDA's recommendation that patients be informed that "some complications associated with the implanted mesh may require additional surgery that may or may not correct the complication." Nowhere in this Clinical Expert Report did Ethicon address the fact that adverse outcomes following the Prolift procedure could result in <u>permanent</u> disability for the patient.

Literature Review, (c) Detailed Findings, continued

- In considering the specific complications, the following summarize the results of this review.

Analysis

1) The following lists complications including mesh erosion of pelvic organ tissues, vesicovaginal or rectovaginal fistulas, material perforations (bladder perforation), perioperative visceral lesions (bladder injury, rectal injury, overall visceral injury), hematoma, dyspareunia, and pain syndrome. As discussed below, far from representing a comprehensive list of concerns regarding the use of implant materials in prolapse repair, this list excludes entire categories of complications due to transvaginal mesh surgery, indicating that at the very least, Ethicon was deficient in its performance of this review, and again raising the suspicion that Ethicon omitted material complications, in order to accomplish the true objective of this report, to present just enough evidence to be able to conclude that Prolift is sufficiently safe to continue marketing (which I do not believe to be true).

Incredibly, this list of complications does not include infection, although infection was listed as an issue or concern regarding the use of implant materials in the stated objective of this Clinical Expert Report. In fact, infection accounted for 13% (25 cases) of the complaints that Ethicon received related to Prolift, recorded as Issue Reports.[800] Infectious complications of the Prolift procedure span the gamut from frequent but less serious, such as urinary tract infection (unless urinary tract infections become frequent or recurrent, which would then be serious), to serious albeit treatable, such as abscess formation,[801] to less common but life-threatening infectious complications, such as sepsis and necrotizing fasciitis.[802]

The earliest reports of vaginal mesh implantation for prolapse repair, even without mesh arms, described pelvic abscess formation, requiring mesh removal and invasive procedures for drainage.[803] In fact, the authors of this article concluded that the morbidity with use of polypropylene mesh in vaginal prolapse repair was so high, **"We believe that the use of prolene mesh should be abandoned."**

Because vascular injury is a common complication due to the blind passage of the Prolift trocars, hematomas are a frequent postoperative complication. Hematomas easily develop into abscesses, given the favorable environment in a hematoma for bacterial growth and the inevitable contamination at the time of vaginal surgery. From medical literature reports of complications due to the TVT and TVT-O, Ethicon knew that abscess formation occurred and, even worse, spread outside the pelvis, apparently along the tracts created by the mesh arms. Again, this serves to emphasize that, in marked contrast to traditional vaginal prolapse surgery and even use of Gynemesh PS mesh in vaginal prolapse surgery, the Prolift procedure caused the introduction of an entirely new category of serious complications outside of the pelvis and

[800] Note that Prolift Issue Reports reviewed only cover the time period of March 2005 to June 2009 and do not represent a complete listing of all Issue Reports generated during that time.
[801] ETH-08343; ETH-08410; ETH-10127; ETH-09853; ETH-08926; ETH-08894
[802] ETH-08776; ETH-00639; ETH-10127; ETH-09541
[803] ETH-60173: Milani R et al. Functional and anatomical outcome of anterior and posterior vaginal prolapse repair with prolene mesh. BJOG Jan 2005; 112: 107-111.

involving structures that were previously healthy and unaffected by prolapse. This Prolift Clinical Expert Report failed to address this issue at all.

Of further concern, some reports in the medical literature described the development of severe infectious and other mesh-related complications remote from the index surgery, again emphasizing that there is no "safe" time after permanent mesh implantation; the risk for complications is LIFE-LONG. Again, this Prolift Clinical Expert Report failed to address this issue at all.

2) Moreover, the only mesh-related complication in this list is mesh erosion; Ethicon failed to include other significant Prolift mesh-related complications, particularly mesh retraction.

3) Although one sentence in the perioperative visceral lesions section deals with overall visceral injury, Ethicon failed to include ureteral injury and ureteral obstruction.

4) Urinary complications were not included, such as urinary retention, voiding dysfunction, stress and urge urinary incontinence, urgency, frequency, and dysuria.

5) Bowel complaints were not included, such as dyschezia (pain with bowel movements), obstructed defecation due to Prolift mesh contraction over the rectum, and fecal urgency and incontinence.

6) Nerve injury and neurological deficits were not included, although "nerve damage/pain" and "neurological deficits" accounted for 12% (23 cases) of the internal Ethicon complaints related to Prolift.

7) Intraoperative hemorrhage or vascular injury was not included, only hematoma as a subset of the types of bleeding complications that occur due to Prolift.

8) Recurrent prolapse was not included. This is of particular importance, given the difficulty of reoperating in the spaces where the Prolift mesh implants exist, along with the scarring and chronic inflammatory and foreign body reaction that the Prolift mesh incites. In addition, Ethicon failed to address the issue of recurrent prolapse specifically due to Prolift mesh contraction.

Literature Review, (c) Detailed Findings, continued

- Mesh Erosion of pelvic organ tissues

o Erosions are, by incidence, the single most important complication that the use of synthetic graft reinforcements has introduced in pelvic floor surgery. Erosion rates range from

3.2 to 19.3% depending on the compartment receiving the graft reinforcement and the particular mesh employed.

Analysis

1) By labeling this section as "mesh erosion of pelvic organ tissues," Ethicon apparently did not distinguish between vaginal mesh exposure, serious enough in its own right, versus visceral mesh erosion, that is even more serious.

2) Ethicon failed to provide any citations for the stated range of mesh erosion.

3) Although Ethicon claimed that the frequency of mesh erosion depended on the compartment and mesh type, no further information was provided to elucidate the importance of this finding.

- Mesh Erosion of pelvic organ tissues, continued

o The study by Abdel Fattah et al in The BJOG of 2008, also noted higher mesh excision rates in total procedures. … erosion rate correlates to the bulk of mesh utilized in the repair. …

Analysis

Ethicon failed to fully describe the important findings of the cited article,[804] which included vaginal mesh exposure in 30 women (10.4%); symptomatic in all but 1 woman with offensive vaginal discharge in 29 women and dyspareunia in 8 women; requiring surgical management in all women despite initial local treatment with estrogen or antibiotics; partial mesh excision in 28 of 30 women, with 4 women requiring 2 procedures; and 2 women with massive erosion, infection, and pain who required complete mesh removal. In addition, 1 woman had mesh erosion into the bladder, requiring laparotomy and partial cystectomy (removal of the bladder). This is yet another example of Ethicon's common practice of selectively reporting bits of data while ignoring other evidence, particularly the type of evidence that demonstrates clearly the magnitude and severity of complications caused by the Prolift product and procedure.

- Mesh Erosion of pelvic organ tissues, continued

o A comprehensive review [of abdominal sacrocolpopexy] by Nygaard reported 70 erosions in 2178 patients (3.4%). [Nygaard 2004] …

[804] ETH-02608: Abdel-fattah M et al. Retrospective multicentre study of the new minimally invasive mesh repair devices for pelvic organ prolapse. BJOG 2008; 115: 22-20.

o Many of these erosions are asymptomatic and a large proportion of them can be easily managed by local estrogen application and/or partial excision during an office visit. The study by Elmer reported a fairly high mesh exposure rate, however, only a surgical re-intervention rate to excise the exposed mesh in 2.8%. [Elmer 08] Similarly, Hinoul reported a 10.4% exposure rate and a 4.3% intervention rate to excise the mesh partially. [Hinoul]

Analysis

1) Ethicon provided no citations to support their claim that "many" erosions are asymptomatic. Despite the stated objective of the literature review "to provide the most current, documented clinical experience as insight into" complications including erosion, Ethicon made no attempt to document how many women are symptomatic with mesh erosions, and instead claimed that "many" are asymptomatic, in its ongoing attempts to minimize the clinical importance of this frequent complication of transvaginal Prolift mesh implantation.

2) Ethicon provided no citations to support their claim that "a large proportion" of mesh exposures can be managed with vaginal estrogen and/or in-office partial mesh excision. Again, as discussed above, in brazen disregard of the stated objective of the literature review, Ethicon made no attempt to document how women with mesh erosion are actually treated, preferring instead to make self-serving statements that attempt to minimize the severity of the clinical consequences associated with Prolift mesh exposure.

3) Ethicon failed to fully describe the important findings in the Elmer article,[805] including Prolift mesh-related complications in more than half of 243 women 2 months after surgery and in more than one-quarter of 232 women 1 year after surgery. Two months after Prolift mesh implantation, 128 women (53%) had mesh-related complications, including 73 women with granulomas, 18 women with rejection, 16 women with erosion, 11 women with necrosis, and 10 women with infection. One year after Prolift mesh implantation, 65 women (28%) had mesh-related complications, including 26 women with erosion, 19 women with granulomas, 12 women with necrosis, and 4 women each with infection and rejection. From this wealth of evidence describing Prolift mesh-related complications, Ethicon claimed that "only" 2.8% of women required surgical re-intervention, which refers to 7 women treated surgically for mesh erosion. Surprisingly, Elmer et al did not report how the remaining mesh-related complications of granulomas, rejection, necrosis, and infection were treated. Nevertheless, this is yet another example of Ethicon's practice of selective reporting that in no way represents a fair and balanced portrayal of the article's findings.

4) In citing the Hinoul article,[806] Ethicon again selectively reported from those few articles that seemed to minimize the occurrence and clinical severity of mesh erosion. Hinoul et

[805] PLTMEDLIT00571: Elmer C et al. Trocar-guided transvaginal mesh repair of pelvic organ prolapse. Obstet Gynecol 2009 Jan; 113: 117-126.
[806] ETH-02750: Hinoul P et al. A prospective study to evaluate the anatomic and functional outcome of a transobturator mesh kit (Prolift anterior) for symptomatic cystocele repair. J Minimally Invasive Gynecol 2008; 15: 615-620.

al reported a small case series (48 patients) with short-term follow-up (median, 7 months). Again, this stands in stark contrast to the stated objective of the literature review and again emphasizes Ethicon's practice of misrepresenting the medical literature to suit its own purposes, rather than providing a fair and balanced interpretation of the entirety of the medical literature.

Literature Review, (c) Detailed Findings, continued

- Vesicovaginal or rectovaginal fistula

o There are very few abstracts reporting on the development of a fistula … One fistula has been reported upon [sic] in 1695 Prolift patients upon whom complications were reported (erosions excepted), 1 in 670 TVM patients, and 2 in 1,611 unspecified polypropylene meshes. The retrospective review of 684 TVM procedures revealed two vesicovaginal fistulas and one rectovaginal fistula (0.44%). [Caquant]

Analysis

1) Again, Ethicon failed to provide a comprehensive literature review to determine the frequency of one of the most severe complications that occurs after transvaginal mesh surgery, fistula formation.

2) Ethicon failed to provide citations for the sentence reporting fistulas in 1 of 1695 Prolift, 1 of 670 TVM, and 2 of 1611 patients, making it impossible to verify the source of these data.

3) Ethicon ignored the findings of Diwadkar et al[807] (although Ethicon cited Diwadkar elsewhere in this report), who reported that fistula formation was at least twice as frequent after vaginal mesh kits versus traditional prolapse surgery. Fistula formation occurred after mesh kits in a weighted average of 0.2% of cases (95% CI, 0.1-0.4; range, 0-4.2%), versus 0.1% (95% CI, 0-0.1; range, 0-1.5%) after traditional vaginal prolapse surgery and 0.0% (95% CI, 0-0.07; range, 0-0.8) after sacral colpopexy.

Literature Review, (c) Detailed Findings, continued

- Material perforations

o The incidence of bladder perforations though small appeared to receive more attention in 2009 abstracts. Reported occurrences ranged from 2.8% to 7.7%. Comparative methods were not used in any of these reports, but qualitative conclusions suggested these were

[807] PLTMEDLIT00139: Diwadkar GB, Barber MD, Feiner B, Maher C, Jelovsek JE. Complication and reoperation rates after apical vaginal prolapse surgical repair: a systematic review. Obstet Gynecol 2009 Feb; 113: 367-373.

associated more closely with the underlying surgical approach and tissue exposure than with the use of mesh for the POP repair.

Analysis

1) The range of bladder perforations reported here exceeds the range reported earlier in this report, where bladder perforations were reported to the most frequently reported complication, besides mesh erosion, ranging from a mean of 1.8% to 3.8%.[808] The upper range of the percentage cited above, 7.7%, is nearly twice as high as the upper range earlier reported, 3.8%, which introduces questions into exactly how Ethicon performed the "systematic" literature compilation and calculated these ranges of bladder perforation.

2) In contrast to the section on rectal injury during the Prolift procedure, in this section (and the other 2 sections that discuss bladder injury), Ethicon failed to include any information regarding steps surgeons could or should take to detect and appropriately manage bladder injury. Neither the original Prolift IFU nor the Prolift surgical technique document contain any information about the use of cystoscopy to detect and manage bladder injury.[809] The revised Prolift IFU contains a statement suggesting cystoscopy[810] but provides no information about the critically important issue of timing to appropriately detect and manage bladder injury in such a way as to minimize bladder damage (after trocar insertion and before Prolift mesh implantation).

3) Ethicon implied that the "underlying surgical approach" was responsible for the bladder injuries, rather than the use of mesh for prolapse repair. This is a specious argument. The Prolift procedure is markedly different compared with traditional vaginal prolapse surgery, and one of the differences is related to vaginal dissection. Anterior vaginal dissection for the Prolift procedure occurs in the vesicovaginal space, where the risk of bladder injury is greater compared with dissection for traditional vaginal prolapse surgery, in which dissection takes place between the layers of the vaginal muscularis. Therefore, vaginal dissection for the Prolift procedure is a critical preparatory step for Prolift mesh implantation; even if bladder injury is not directly related to the Prolift mesh itself, it is clearly related to the steps leading to Prolift mesh implantation that are so markedly different than the steps of traditional vaginal prolapse surgery.

Literature Review, (c) Detailed Findings, continued

- Perioperative visceral lesions

[808] Page 12 of 29, ETH.MESH.00306712
[809] ETH.MESH.02345122, ETH.MESH.00419571
[810] ETH.MESH.02341734: "Cystoscopy may be performed to confirm bladder integrity or detect possible bladder or ureteral perforation."

o These lesions are not uncommon. Most of them are located at the level of the bladder with an overall incidence rate for Prolift procedures around 2.2%.

Analysis

It is not clear what is meant by this category, particularly given the previous category of "material perforations," that refers to bladder perforation. Again, the "incidence" of 2.2% is not consistent with that reported above for bladder perforation, of 2.8% to 7.7%, or that reported earlier in the report of 1.8% to 3.8%.

Literature Review, (c) Detailed Findings, continued

- Perioperative visceral lesions (continued)

o Rectal lesions are far less common. Only one was described in 937 Apogee patients and 1 in 854 IVS patients. Two PubMed cited studies in Scandinavia reported 4/248 [1.6%] and subsequently 1/252 rectal lesions [0.4%] following Prolift procedures. [Altman, Elmer] These rates seem high in both studies compared to other reports. A rectal examination is recommended after every posterior kit procedure to identify any perforations of the rectum preoperatively. Surgeons are advised to abandon mesh placement (posteriorly) when this occurs.

Analysis

1) Again, Ethicon made no effort to document the true risk of rectal injury through a comprehensive literature review.

2) Ethicon provided no citations for the sentence describing rectal injury in 1 in 937 Apogee cases and 1 in 854 IVS cases, making it impossible to check the sources of these data.

3) Ethicon cited the frequency of rectal injury, 1.6% and 0.4%, from 2 published articles and indicated that these rates "seem high" compared to other reports. However, Ethicon apparently made no effort to understand any reasons behind the apparent difference in reported frequency of rectal injury.

4) Ethicon stated that a rectal examination was recommended after every posterior kit procedure to identify any rectal perforations "preoperatively." The term "preoperatively" is undoubtedly an error; the correct term is "intraoperatively." Ethicon failed to disclose that the Prolift IFU did NOT contain this recommendation for 4-½ years, from March 2005 until October 2009, when the Prolift IFU revised after FDA review was finally released nearly 1-½ years after FDA completed its review.

Moreover, even when the recommendation for rectal examination was included in the revised Prolift IFU, Ethicon failed to address the critically important issue of appropriate timing

of the rectal examination, after trocar placement and before Prolift mesh implantation. Rectal examination after Prolift mesh implantation will detect rectal injury, i.e., Prolift mesh implantation in the rectum, but the requirement for Prolift mesh removal from the rectum causes substantially more tissue damage than if the rectal injury had been detected with the Prolift trocar in place. Ethicon received several complaints that documented this exact sequence of events,[811] yet Ethicon failed to address this issue and inform surgeons of the appropriate steps of detection and management of rectal injury. Furthermore, Ethicon knew of at least one complaint where Prolift mesh was implanted over unrecognized rectal injury, causing life-threatening sepsis and need for colostomy.[812]

Furthermore, since the Prolift surgical technique document recommends against permanent Prolift mesh implantation after rectal injury, this has a substantial effect on intraoperative and postoperative risks and management (performing an alternative procedure instead of Prolift, postoperative antibiotic and bowel management, risk of rectovaginal fistula development, etc). The Clinical Expert Report did not address any of these important clinical consequences of rectal injury.

Literature Review, (c) Detailed Findings, continued

- Perioperative visceral lesions (continued)
  - The overall visceral injury rates compare favorably to the rates encountered when performing a sacrocolpopexy with average rates for its occurrence of 1.7% and 1.1% after sacrocolpopexy and mesh kit respectively. [Diwadkar]

Analysis

1) Again, Ethicon used selective reporting to claim that overall visceral injury rates occur in an average of 1.1% of cases, when in the same report, Ethicon has cited a range of frequency of bladder injury up to 7.7%.

2) As noted above, here Ethicon cited Diwadkar et al[813] by selecting only one category of complications, while ignoring others that showed higher rates of complications with mesh kits. This selective reporting reflects Ethicon's bias in attempting to claim that complications with the Prolift mesh kit are comparable to complications with traditional prolapse surgery, when this is emphatically NOT the case. Even among complication rates that may appear numerically similar, as Ethicon quoted above for perioperative visceral lesions, the clinical consequences of such injuries differs markedly between the Prolift procedure and traditional prolapse surgery. As one example, Ethicon recommends against Prolift mesh

[811] ETH-08217; ETH-08530; ETH-08539; ETH-08866; ETH-09124; ETH-09378; ETH-09755
[812] ETH-00639
[813] PLTMEDLIT00139: Diwadkar GB, Barber MD, Feiner B, Maher C, Jelovsek JE. Complication and reoperation rates after apical vaginal prolapse surgical repair: a systematic review. Obstet Gynecol 2009 Feb; 113: 367-373.

implantation after visceral injury, due to the higher risk of subsequent complications, particularly fistula formation; no such proscription applies for traditional vaginal prolapse surgery.

3) Similar to the discussion above regarding rectal injury during the Prolift procedure, a parallel situation exists for bladder injury and Ethicon's failure to inform surgeons of the most appropriate method of detection and management. As detailed in this report, bladder injury occurs frequently during the Prolift procedure, either during anterior vaginal dissection in the vesicovaginal space or during blind passage of the 4 anterior trocars that pass within millimeters of the bladder. The original Prolift IFU, in effect for 4-½ years from March 2005 to October 2009, did not contain any recommendation as to the need to perform cystoscopy during the Prolift procedure to detect and appropriately manage bladder injury, although the Prolift surgical technique document recommended against placement of the Prolift mesh implant when bladder injury occurred.

4) Moreover, even after FDA review, when Ethicon finally included a statement about cystoscopy in the revised Prolift IFU, it was worded as a suggestion, not as a requirement.[814] Furthermore, Ethicon failed to provide adequate guidance to surgeons as to the critically important issue of timing of cystoscopy, after trocar placement and before Prolift mesh implantation, to limit the bladder damage incurred during the Prolift procedure. Cystoscopy after Prolift mesh implantation will detect bladder injury, i.e., Prolift mesh implantation in the bladder, but the requirement for Prolift mesh removal from the bladder causes substantially more tissue damage than if the bladder injury had been detected with the trocar in place. Ethicon received several complaints that documented this exact sequence of events,[815] yet Ethicon failed to address this issue and inform surgeons of the appropriate steps of detection and management of bladder injury.

5) Moreover, since the Prolift surgical technique document recommends against permanent Prolift mesh implantation after bladder injury, this has a substantial effect on intraoperative and postoperative risks and management (performing an alternative procedure instead of Prolift, postoperative antibiotic and catheter management, risk of vesicovaginal fistula development, etc). The Clinical Expert Report did not address any of these important clinical consequences of bladder injury.

6) Furthermore, nowhere in the Clinical Expert Report is the risk and frequency of immediate ureteral injury and postoperative ureteral obstruction addressed.

Literature Review, (c) Detailed Findings, continued

[814] ETH.MESH.02341734, revised Prolift IFU: "Cystoscopy may be performed to confirm bladder integrity or detect possible bladder or ureteral perforation."
[815] ETH-08071; ETH-08163; ETH-00495; ETH-08776; ETH-08794; ETH-09252; ETH-09655; ETH-09677; ETH-10019; ETH-09988

- Hematoma

o Hematomas are commonly reported in the IUGA series in approximately 3% of mesh kit procedures. Rarely are transfusions required. As vascular injuries can be life threatening, despite their rare occurrence, 4 case reports following Prolift have been published. Two of them were self limiting, one required embolization of the internal iliac artery and the other was an injury of the internal iliac vein which required embolization and packing. In the PubMed literature the series of Abdel Fattah included two significant vascular injuries: one to the right pudendal artery requiring suturing and 5 units of packed cells and one lesion to the uterine artery requiring embolization and transfusion with 4 units of packed cells. No other reports of life threatening vascular injuries could be identified. Here too, the comparison to traditional repairs and sacrocolpopexies is favorable; based on Diwadkar's review the weighted averages are 2.8%, 1.6% and 1.1%, for traditional repairs, sacrocolpopexy and mesh kits respectively.

Analysis

1) Here, Ethicon described a frequency of 3% as common, in contrast to its claims that complications due to the Prolift product and procedure are "rare."

2) Ethicon provided no citations for the 3% figure for hematomas, referring only to the IUGA series. Ethicon provided no evidence for the claim that transfusions were "rarely" required.

3) Again, Ethicon cited the review by Diwadkar et al by selectively reporting one of the complications, and nowhere in the Clinical Expert Report did Ethicon address the overall findings of this review, that complications due to mesh kits were <u>common</u> at 14.5% (NOT rare), most complications due to mesh kits required surgical treatment under general anesthesia (Dindo grade IIIb), and the total reoperation rate of 8.5% was highest in comparison to traditional vaginal prolapse surgery and sacral colpopexy despite having the shortest follow-up.[816]

Literature Review, (c) Detailed Findings, continued

- Dyspareunia

Dyspareunia is a more problematic outcome measure to assess than might be expect [sic]. Not all authors account for the actual number of sexually active patients in their study. Secondly some patients may not be sexually active before surgery due to the prolapse and others may have become sexually inactive after surgery due to the procedure (certainly when assessing short term follow up < 6 months) or unrelated factors (partner's impotence, lack of desire). A study specifically addressing the dyspareunia issue after Prolift by Lowman in the AJOG of 2008

[816] PLTMEDLIT00139: Diwadkar GB, Barber MD, Feiner B, Maher C, Jelovsek JE. Complication and reoperation rates after apical vaginal prolapse surgical repair: a systematic review. Obstet Gynecol 2009 Feb; 113: 367-373.

identified a high de novo dyspareunia of almost 17% after Prolift. [Lowman] Surprisingly, studies after sacrocolpopexy yielded de novo dyspareunia rates as high as 15 and 19%. [Handa, Claerhout] A report by a tertiary referral center on 22 patients treated for complications following all types of mesh surgeries to treat prolapse over a period of almost 4 years stated that the most common symptom in 10/22 patients was dyspareunia. [Blandon 2009]

…

Traditional repairs are associated with 19% of de novo dyspareunia rates [Weber] and associating a levator ani placation [sic] would increase the incidence to 27%. [Kahn] Performing a midline fascial placation [sic] or a discrete fascial repair in a comparative study yielded similar dyspareunia rates of 14 and 19%. [Abramov] Finally, the sacrospinous ligament fixation has been associated with de novo dyspareunia rates as high as 36%. [Maher]

Analysis

1) Ethicon cited one article that reported 17% new dyspareunia after the Prolift procedure,[817] again using selective reporting rather than a comprehensive literature review. Ethicon provided no qualitative analysis of the findings of the cited article. Oddly, the authors of the cited article decided that chart review (6 of 36 patients, 17%) was more reliable than patient questionnaires (13 of 41 patients, 32%) in assessing the development of new dyspareunia after the Prolift procedure. The actual rate when appropriately calculated is even higher. Considering that at least one of the authors of the cited article had been (and may still be) a consultant for Ethicon, this decision may be affected by financial conflict of interest. None of the authors disclosed conflicts of interest in the cited article.

2) Ethicon went on to cite selected articles that reported dyspareunia after sacral colpopexy and traditional vaginal prolapse surgery, again demonstrating Ethicon's practice of selective reporting rather than providing a fair and balanced assessment of the body of literature that has been published.

3) Ethicon failed to disclose the marked difference in the ability to effectively treat dyspareunia after prolapse surgery. Dyspareunia after traditional vaginal prolapse surgery may occur if the vagina is narrowed. This can be effectively treated with vaginal dilators (often used with vaginal estrogen), as the vagina is fully capable of stretching after traditional vaginal prolapse surgery. If that strategy is not successful, it is possible to perform a minor (outpatient) surgery in which "relaxing" vaginal incisions are made to increase vaginal capacity. In this way, when dyspareunia occurs after traditional vaginal prolapse surgery, it can be effectively treated while incurring very little additional morbidity for the patient.

In stark contrast, dyspareunia after the Prolift procedure, particularly after the total Prolift mesh implantation, is a completely different situation. Authors have described that the encircling Prolift mesh creates a "condom-like" effect around the vagina, preventing normal expansion with

[817] ETH-02345: Lowman JK, Jones LA, Woodman PJ, Hale DS. Does the Prolift system cause dyspareunia? Am J Obstet Gynecol 2008 Dec; 199: 707.e1-6. Epub 2008 Nov 5. Presented at SGS, April 2008.

sexual arousal.[818] Other authors reporting sexual dysfunction after the Prolift procedure have commented that "In a predominantly parous and postmenopausal population, stage 0 may be considered a surgical overcorrection of vaginal anatomy. Anatomical overcorrection and tautness of the mesh may compromise vaginal elasticity, give rise to vaginal tension, and prevent swelling of the vagina at sexual arousal."[819]

General treatment of dyspareunia after the Prolift procedure has not been described in the literature. One specific type of dyspareunia after the Prolift procedure is caused by the development of Prolift mesh bands, commonly across the anterior and/or posterior vagina where the mesh arms join the mesh body.[820,821,822] As Prolift mesh contraction occurs, a ridge of firm and painful tissue is raised across the transverse dimension of the vagina. Surgical treatment is required to release and excise the mesh bands, adding another incident of surgical morbidity; unfortunately, due to the chronic inflammatory and foreign body reaction incited by the permanent Prolift mesh, and the effects of subsequent surgeries, contraction and scarring continues to occur and perpetuates the vicious cycle causing dyspareunia.

So high is the concern of creating severe and major new morbidity after mesh implantation that some surgeons will not even attempt surgical treatment, despite failure of all conservative measures to obtain symptom relief.[823] This high level of concern is certainly warranted; for example, in a case series describing 21 patients with severe complications after transvaginal mesh implantation, in one woman who had already undergone previous surgery, attempted mesh excision resulted in significant blood loss requiring transfusion, rectotomy (unplanned cut into the rectum), intestinal diversion, and intensive care unit admission.[824] Subsequently, this patient developed a ureterovaginal fistula, failed stent management, and required ureteroneocystotomy (reconnection of the ureter to the bladder). Nowhere in this Clinical Expert Report is this type of complication described, where a single patient experiences a series of major complications, all ultimately due to the Prolift procedure and permanent Prolift mesh implantation and the need for multiple surgeries that result in a cascade of morbidity.

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[818] Su TH, Lau HH, Huang WC, et al. Short term impact on female sexual function of pelvic floor reconstruction with the Prolift procedure. J Sex Med 2009; 6: 3201-3207

[819] PLTMEDLIT-00564: Altman D, Elmer C, Kiiholma P, et al. Sexual dysfunction after trocar-guided transvaginal mesh repair of pelvic organ prolapse. Obstet Gynecol 2009; 113: 127-133.

[820] ETH-02345: Lowman JK, Jones LA, Woodman PJ, Hale DS. Does the Prolift system cause dyspareunia? Am J Obstet Gynecol 2008 Dec; 199: 707.e1-6. Epub 2008 Nov 5. Presented at SGS, April 2008.

[821] ETH-51072: Walid MS, Heaton RL. Laparoscopic apical mesh excision for deep dyspareunia caused by mesh banding in the vaginal apex. Arch Gynecol Obstet 2009 Sep; 280: 347-350. Epub January 7, 2009.

[822] ETH-02290: Boyles SH, McCrery R. In the Trenches: dyspareunia and mesh erosion after vaginal mesh placement with a kit procedure. Obstet Gynecol April 2008; 111: 969-975.

[823] PLTMEDLIT00712: Lin LL et al. Dyspareunia and chronic pelvic pain after polypropylene mesh augmentation for transvaginal repair of anterior vaginal wall prolapse. Int Urogynecol J 2007; 18:675-678. Epub September 20, 2006.

[824] PLTMEDLIT00844: Blandon RE et al. Complications from vaginally placed mesh in pelvic reconstructive surgery. Int Urogynecol J 2009; 20:523-531. Online February 10, 2009.

Literature Review, (c) Detailed Findings, continued

- Pain Syndrome

The incidence in the PubMed literature varies widely from 1.2% to 6.4%. A review of reoperations for complications following mesh surgery in a tertiary referral centre identified 13 patients. The primary complaint in 9 of those 13 patients (69%) was vaginal pain; 85% suffered from mesh exposure. Two contributing factors identified by this team for these two complications were mesh folding, which was identified in 9 of 13 patients during surgical exploration, and mesh shrinkage. As normal urinary, sexual and defecatory functions require a compliant vagina, excessive stiffness can lead to dyspareunia, defecatory and urinary dysfunction.[825] Also of note in this article on 13 complications was that the median time from mesh surgery to presentation was 8 months (1-16 months) and that a median of 2 additional procedures were required to achieve acceptable results. A similar report by a tertiary referral center on 22 patients treated for complications following all type of mesh surgeries to treat prolapse over a period of almost 4 years stated symptoms other than dyspareunia included chronic vaginal drainage in nine patients, pain not related to intercourse in 7.[826] In 14 patients, pain could be elicited on vaginal palpation.

One of their most important findings is that only 14% of patients were referred by the original surgeon, suggesting a lack of awareness of these complications by the original treating physician and the potential for underreporting of the rate and extent of these complications due to non-respondent/volunteer bias. The authors, however, fail to recognize that 22 cases for many different types of procedures is not a very high number of patients considering the magnitude and authority of the tertiary referral centre reporting upon this series.

Analysis

1) Ethicon provided no citations for its statement about the incidence of pain syndrome. Ethicon provided no definition for what constitutes a pain syndrome.

2) By the time of this Clinical Expert Report, experienced Prolift users considered that the Prolift procedure was relatively contraindicated, if not absolutely contraindicated, in women with a pre-existing chronic pain condition, because these women developed chronic pain caused by the Prolift procedure and/or an exacerbation of their existing pain condition more frequently than women without pre-existing pain.[827,828,829] However, Ethicon did not include that

[825] [Margulies 2008]
[826] [Blandon 2009]
[827] Roundtable: Using mesh to repair prolapse calls for more than a kit – it takes skill. Karram MM, moderator. OBG Management 2009; 21 (1): 25-36. Dr. Lucente: "At our center, because the potential for dyspareunia and pelvic discomfort is our biggest concern, we have developed a profile of the patient who is more likely to develop these complaints. The profile includes any patient who has a chronic pain disorder of any type, but especially chronic pelvic pain disorders such as endometriosis and vulvodynia. Other risk factors appear to be a history of pelvic surgery involving any permanent material, suture or mesh, and young age. So if we have a patient in her late 30s

extremely important criterion of patient selection in this Clinical Expert Report, and Ethicon never changed the Prolift IFU, physician marketing materials, or patient marketing materials to include this information. In fact, far from informing patients with pain about their higher risk of the Prolift procedure, Ethicon marketed directly to these patients, promising that Prolift would relieve their pain.[830]

3) Ethicon attempted to minimize the importance of the Blandon et al report by claiming that 22 cases "is not a very high number of patients." These patients represent the "tip of the iceberg" in terms of the severity and refractory nature of their complications, and that many more patients experience complications to a similar degree that do not get reported in the medical literature.

4) Ethicon ignored the importance of the finding that few of the original treating surgeons were aware of these complications, leading to a positively skewed impression of their patients' outcomes among those original treating surgeons. Ethicon ignored the importance of underreporting and bias that drastically affects the reporting of complications outside of a well-designed, well-controlled clinical study.

Literature Review, (c) Detailed Findings, continued

- In summary, notwithstanding the attention clinicians, the U.S. FDA, the Cochrane Database of Systematic Reviews and NICE have given to the question of complications associated with synthetic mesh used in pelvic organ prolapse surgery, the complication rate is considered "rare" and for in stances [sic] can be minimized through specialized training (Urogynecology) and meticulous surgical technique. Furthermore, when complications are encountered thorough awareness and immediate action also lessens severity. Additionally, based on the experiences cited by numerous researchers, the more serious complications (sans mesh

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who has undergone reconstructive surgery using permanent sutures and who has an element of chronic pelvic pain, we would counsel her strongly to consider surgical options other than the use of synthetic mesh."

[828] ETH.MESH.00067358, Webinar featuring Dr. Lucente, 12-15-2008: "I think we need to still be cautious of what we know about who are not, perhaps, ideal candidates for this. In our literature in our series points to the 3 areas that increase the likelihood of pain and that is a patient of younger age … Secondly, as a patient who's had a prior pelvic surgery with a permanent material being utilized, be it suture or graft, and third category we've identified is a chronic pain disorder of any type. …"

[829] ETH-85676, email from Dr. Butrick to David Robinson, 1-20-2007, myofascial pain after Prolift: "I sure am tired of seeing these pts with bad myofascial pain after Prolifts. The doctors need to be taught how to identify pf [pelvic floor] pain disorders and avoid placing meshes thru these spastic muscles. It only gives the kits a bad name." ETH-85678, slide submitted by Dr. Butrick for Prolift Summit case study, patients with postoperative pain: "I have at least 4 pts with this problem sent to me. I feel that the pts start w/ mild POP and PFTM [pelvic floor tension myalgia]. The aggressive surgery flares the pre-exsisting [sic] myofascial pain. WE should therefore review with our doctors the difference between POP and "pressure" of PFTM. POP does not cause pain!!! Look for symptoms >> degree POP."

[830] ETH-48130, Prolift advertising directed to patients, copyright 2007. Large font heading: "One day you have pelvic pain. The next day you don't. Imagine that." "It [the cause of pelvic pain] may be pelvic organ prolapse." "And it [the Prolift procedure] can restore pelvic support and end the pain …"

erosion) occur no more frequently with mesh than in the traditional prolapse treatment techniques. And, finally, mesh use is associated with higher prolapse cure success rates, at least in the follow-up periods that are currently available.

Analysis

1) In one phrase, Ethicon dismissed the serious concerns about mesh-related complications raised by clinicians, the FDA, the Cochrane review, and NICE. Despite Ethicon's wording, there is no "question" about the frequency and severity of complications associated with synthetic mesh used in vaginal prolapse surgery.

2) Despite accumulating evidence of the frequency and severity of complications due to the Prolift procedure, Ethicon continued to claim that "the complication rate is considered 'rare'." Only extreme bias could allow anyone to conclude that complications are "rare" after the Prolift procedure.

3) Despite Ethicon's claim that Prolift complications "can be minimized through specialized training," the evidence clearly contradicts this claim.

4) Despite Ethicon's claim that Prolift complications can be minimized with "meticulous surgical technique," again, the evidence clearly contradicts this claim.

5) Ethicon went on to claim that "when complications are encountered, thorough awareness and immediate action also lessens severity." Ethicon itself withheld critically important information from surgeons that impaired their "thorough awareness" of the range and severity of complications to be expected during and after the Prolift procedure. Moreover, Ethicon withheld critically important information from surgeons that impaired their ability to appropriately detect and manage complications during and after the Prolift procedure.

6) Ethicon's claim that more serious complications, with the exception of mesh erosion, occur no more frequently with mesh than in traditional prolapse surgery is contradicted by strong evidence in the medical literature. As only one example, a systematic review of almost 17,000 patients reported the highest total reoperation rate after vaginal mesh kits, despite the shortest follow-up.[831] In addition, complications with vaginal mesh kits most often required surgical intervention under general anesthesia (Dindo grade IIIb). Moreover, Ethicon ignored other more serious mesh-related complications, particularly mesh retraction and its constellation of associated symptoms and comorbidities, and Ethicon ignored the added risk of trocar-related complications that do not occur with traditional prolapse surgery. Furthermore, Ethicon ignored the entirely new category of complications due to the Prolift procedure and permanent Prolift mesh implantation in non-vaginal, non-pelvic tissues that were previously healthy and unrelated to the prolapse.

[831] PLTMEDLIT00139: Diwadkar GB, Barber MD, Feiner B, Maher C, Jelovsek JE. Complication and reoperation rates after apical vaginal prolapse surgical repair: a systematic review. Obstet Gynecol 2009 Feb; 113: 367-373.

7) Finally, Ethicon claimed that mesh use is associated with higher prolapse cure rates, at least with currently available follow-up. First, the "higher cure rates" only apply to anterior vaginal prolapse, and the evidence to support even that claim is weak. Second, the evidence shows no difference in outcomes of importance to patients. Third, Ethicon ignored data that showed substantial deterioration in "cure rates" for transvaginal mesh surgery over time.

D. Literature Review Conclusion Statement

The above data, taken together with any available pre-clinical data, are sufficient to demonstrate compliance with the essential requirements covering safety and performance of Gynecare Prolift total, anterior, and posterior Pelvic Floor Repair Systems under normal conditions of use. No additional data is required.

Analysis

1) Without any citation to evidence, Ethicon referred to "available pre-clinical data" that supposedly demonstrates safety and performance of the Prolift Systems. Given that Ethicon never performed any pre-clinical testing when Gynemesh PS mesh was applied to prolapse repair from hernia repair,[832] it is a mystery as to what data Ethicon referred to.

2) Ethicon concluded that no additional data were required, ignoring the strongly worded conclusions of many of the cited articles in this report, that further data are "mandatory,"[833] "required,"[834] and "needed"[835] before "transvaginal meshes can be accepted as routine surgery"[836] or "used in routine clinical practice."[837]

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[832] ETH.MESH.01160159, Gynemesh Prolene Soft mesh, pre-clinical functionality testing strategy, 11-1-2001: "The clinical tissue compatibility of Gynemesh Prolene Soft mesh is essentially equivalent to Prolene mesh since the Gynemesh Prolene Soft mesh is chemically unchanged from Prolene mesh and sutures." Conclusion: "Based upon the Gynemesh Prolene Soft mesh's product characteristics, intended clinical indications and the use of existing polymer materials, additional pre-clinical functionality testing is not required."

[833] PLTMEDLIT00068: Feiner B, Jelovsek JE, Maher C. Efficacy and safety of transvaginal mesh kits in the treatment of prolapse of the vaginal apex: a systematic review. BJOG 2009; 116: 15-24. "Further research addressing functional outcomes and the impact of these procedures on women's symptoms and quality of life is mandatory."

[834] PLTMEDLIT00154: Jia X et al. Efficacy and safety of using mesh or grafts in surgery for anterior and/or posterior vaginal wall prolapse: systematic review and meta-analysis. BJOG 2008; 115: 1350-1361. Epub August 19, 2008. "Rigorous long-term RCTs are required to determine the comparative efficacy of using mesh/graft."

[835] PLTMEDLIT00174: Sung VW et al. Graft use in transvaginal pelvic organ prolapse repair: a systematic review. Obstet Gynecol November 2008; 112: 1131-1142. "Adequately powered randomized trials evaluating anatomic and symptomatic efficacy as well as adverse events are needed."

[836] PLTMEDLIT01209: De Ridder D. Should we use meshes in the management of vaginal prolapse? Curr Opin Urol 2008; 18: 377-382. "Long-term controlled studies will have to confirm the effectiveness and safety of new mesh and will have to include more functional data on sexuality and quality of life, before transvaginal meshes can be accepted as routine surgery."

E. Complaint/Adverse Event Review

I. Internal complaint review

a. Gynecare Prolift is indicated for tissue reinforcement and long-lasting stabilization of fascial structures of the pelvic floor in vaginal wall prolapse where surgical treatment is intended, either as a mechanical support or bridging material for the fascial defect. The typical environment for its use is within the boundaries of the sterile field of the operating theater of a hospital.

Analysis

Although Ethicon claimed that Prolift is used "within the boundaries of the sterile field," vaginal surgery is not performed in a sterile environment. Surgically, the vagina is considered a clean-contaminated environment, because it cannot be sterilized with antiseptic preparation. In addition, it is not possible to use sterile surgical drapes in such a way that a sterile field is created and maintained throughout vaginal surgery. Bacterial contamination of the permanent Prolift mesh implant is inevitable when placed transvaginally.[838] Ethicon is well aware of these facts, yet attempts to represent the surgical environment under which the permanent Prolift mesh implant is placed as if it is sterile.

Internal complaint review, continued

Complaints for the period 1/2007 thru 5/2010 are summarized in the following table.

(The table lists 13 types of complaints for a subtotal of 186. A number of 238 is labeled "no associate harms," for total of 424 complaints.)

The corresponding volume of units distributed for this same time period equaled 96,438 producing an overall compliant [sic] rate of .0044%.

Analysis

1) In its Complaint Summary, Ethicon failed to report the deaths of 2 patients treated with the Prolift procedure.[839]

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[837] ETH-02608: Abdel-fattah M et al. Retrospective multicentre study of the new minimally invasive mesh repair devices for pelvic organ prolapse. BJOG 2008; 115: 22-20. "Randomised trials comparing these mesh repair kits to the established repair procedures are urgently needed before these procedures can be used in routine clinical practice."

[838] PLTMEDLIT01559: Culligan P, Heit M, Blackwell L, Murphy M, Graham CA, Snyder J. Bacterial colony counts during vaginal surgery. Infect Dis Obstet Gynecol 2003; 11: 161-165.

[839] ETH.MESH.00000081; ETH-09316: A 63-year-old woman underwent posterior Prolift procedure on 12-4-2007, went into respiratory arrest on the same day, and died 18 days later on 12-23-2007. Autopsy reported the cause of death as irreversible cerebral anoxia, pulmonary thrombo-embolism, and deep vein thrombosis.

Both deaths occurred in 2007. One death occurred as a result of uncontrolled bleeding. The second death apparently was caused by pulmonary embolism.

2) Ethicon failed to define or describe the categories of complaints, and Ethicon failed to include a comprehensive list of all types of complications due to the Prolift procedure (see below for further discussion).

3) The review period does not extend back to the launch of Prolift in March 2005. Since no other Prolift Clinical Expert Report had been produced between January 2005,[840] before the launch of Prolift, and the current 2010 report, Ethicon should have included a complete summary of the complaints received for the entire period of Prolift's commercial availability.

During the time period that Ethicon excluded (March 2005 to December 2006), Ethicon received 101 complaints, only half of which (51) were reported to the FDA. Clinical complaints not reported to the FDA included 14 cases of bladder injury,[841] 4 cases of pain,[842] 4 cases of intraoperative mesh tearing,[843] 3 postoperative mesh complications,[844] and 2 cases of hematoma.[845]

4) In comparing the Complaint Summary table with complaints that Ethicon received for Prolift, recorded internally as Issue Reports, there are several discrepancies. From Ethicon-provided documents, I reviewed Prolift Issue Reports from March 2005 (Prolift launch) to June 2009, a time period of 51 months.[846] **NOTE:** The Issue Reports reviewed are not a complete compilation of complaints/Issue Reports over the time periods stated. Therefore, all numbers cited with regard to the Issue Reports represent an underestimate of Issue Reports that Ethicon actually prepared.

The Complaint Summary table in the 2010 Prolift Clinical Expert Report covered January 2007 through May 2010, a time period of 41 months. Although the time periods differ, there is a 30-month overlap, and a comparison of the two time periods should show a similar frequency in numbers of complaints. In any event, there should be no examples where the numbers are markedly different. And, yet, that is exactly what has occurred. As just a few examples, the number of complaints regarding internal organ damage, pain, failure of treatment, and fistula formation are markedly discrepant, suggesting at the very least that Ethicon excluded or miscategorized many complaints.

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[840] ETH-07152
[841] ETH-00613, ETH-00606, ETH-00599, ETH-08623, ETH-08616, ETH-08513, ETH-08382, ETH-08374, ETH-00503, ETH-08260, ETH-08163, ETH-08132, ETH-08108, ETH-08071
[842] ETH-00723, ETH-00400, ETH-00730, ETH-08125
[843] ETH-08120, ETH-08141, ETH-08246, ETH-08253
[844] ETH-00537, ETH-00531, ETH-08157
[845] ETH-00483, ETH-08055
[846] ETH-00400-00734, ETH-08055-10143

The Complaint Summary table identified 15 cases of internal organ damage during the 41-month period from January 2007 to May 2010. However, over the 51-month period from March 2005 to June 2009, Ethicon received a total of 59 Issue Reports of internal organ damage, including 26 cases of bladder injury[847] (only 9 of which were reported to the FDA); 12 reports of rectal injury;[848] and 11 reports of ureteral injury.[849] Ethicon underreported the frequency of internal organ injury.

The Complaint Summary table identified 21 cases of nerve damage/pain, yet Ethicon received a total of 73 Issue Reports of nerve injury and pain, including 43 reports of pain (8 of which were not reported to the FDA);[850] 22 reports of dyspareunia and apareunia (1 of which was not reported to the FDA);[851] and 8 reports of nerve injury (2 of which were not reported to the FDA).[852]

The Complaint Summary table identified 3 cases of failure of treatment, yet Ethicon received a total of 19 Issue Reports of recurrent prolapse, 3 of which were not reported to the FDA.[853]

The Complaint Summary table identified 7 cases of fistula formation, yet Ethicon received a total of 15 Issue Reports of vesicovaginal and rectovaginal fistulas.[854] In the table, it is

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[847] Issue Reports of bladder injury not reported to FDA: ETH-08071; ETH-08108; ETH-08132; ETH-08163; ETH-00490; ETH-00503; ETH-08374; ETH-08382; ETH-08513; ETH-08616; ETH-08623; ETH-00599; ETH-00606; ETH-00613; ETH-09252; ETH-09302; ETH-09406
Issue Reports of bladder injury reported to FDA: ETH-08206; ETH-08260; ETH-00495; ETH-08794; ETH-08776; ETH-00629; ETH-08578; ETH-09988; ETH-10019

[848] ETH-08217; ETH-00639; ETH-08443; ETH-08492; ETH-08530; ETH-08539; ETH-08656; ETH-08866; ETH-09124; ETH-09378; ETH-09755; ETH-09945

[849] ETH-00685; ETH-08563; ETH-08429; ETH-08578; ETH-10040; ETH-09677; ETH-09655; ETH-10019; ETH-08764; ETH-09041; ETH-09763

[850] Issue Reports of pain not reported to FDA: ETH-00400; ETH-00723; ETH-00594; ETH-09406; ETH-09442; ETH-09934; ETH-09973; ETH-08970
Issue Reports of pain reported to FDA: ETH-09110; ETH-09482; ETH-09599; ETH-09623; ETH-09631; ETH-09717; ETH-09926; ETH-10052; ETH-10101; ETH-08875; ETH-09226; ETH-09204; ETH-00467; ETH-00676; ETH-00685; ETH-08483; ETH-08646; ETH-09541; ETH-08998; ETH-08734; ETH-09886; ETH-10079; ETH-08429; ETH-09979; ETH-10069; ETH-08723; ETH-08699; ETH-08914; ETH-09662; ETH-09591; ETH-10088; ETH-08926; ETH-09684; ETH-09080; ETH-09100

[851] Issue Report of dyspareunia/apareunia not reported to FDA: ETH-09497
Issue Reports of dyspareunia/apareunia reported to FDA: ETH-09110; ETH-09239; ETH-09447; ETH-09575; ETH-09647; ETH-09790; ETH-09953; ETH-10113; ETH-08646; ETH-00543; ETH-00665; ETH-08946; ETH-08998; ETH-10069; ETH-09639; ETH-09733; ETH-09052; ETH-09457; ETH-09467; ETH-09583

[852] Issue Reports of nerve injury not reported to FDA: ETH-00730; ETH-08125
Issue Reports of nerve injury reported to FDA: ETH-10113; ETH-08998; ETH-08734; ETH-09886; ETH-08398; ETH-08451

[853] Issue Reports of recurrent prolapse not reported to FDA: ETH-09437; ETH-09246; ETH-00594
Issue Reports of recurrent prolapse reported to FDA: ETH-09607; ETH-09647; ETH-10101; ETH-10119; ETH-00407; ETH-00447; ETH-08326; ETH-09023; ETH-09155; ETH-09355; ETH-09662; ETH-09591; ETH-10088; ETH-09639; ETH-09615; ETH-09677

not clear whether Ethicon categorized fistulas as gastrointestinal erosion (4) or urinary tract erosion (14); at the very least, it suggests that Ethicon miscategorized or misreported the number of these very serious complications.

As the above examples clearly demonstrate, Ethicon apparently excluded a markedly high number of clinically significant complaints from its Prolift complaint summary.

5) Ethicon failed to include a comprehensive listing of categories of complaints in the Complaint Summary table. For example, Ethicon excluded ureteral injury and obstruction, urinary complaints, bowel complaints, allergic reactions, and other/unknown. Ethicon received 59 Issue Reports (11 of which were not reported to the FDA) described by these categories[855] and apparently excluded from the Complaint Summary table.

Moreover, Ethicon only identified mesh-related complaints as exposure/erosion and did not identify other mesh-related complications, particularly mesh contraction. In addition, Ethicon did not identify dyspareunia and apareunia as Prolift complaints and gave no indication whether dyspareunia/apareunia were included in the category of nerve damage/pain. Furthermore, Ethicon apparently excluded 2 patients who experienced life-threatening complications after the Prolift procedure from the Complaint Summary table.[856]

6) Ethicon provided no explanation for the 238 complaints labeled as "no associate harms."

7) Ethicon misreported the percentage of complaints per units distributed by a factor of 100. The correct percentage is 0.44%, not 0.0044%. Moreover, this is a specious calculation. Ethicon was well aware that its complaint summary represented marked underreporting

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[854] Vesicovaginal fistulas = 6: ETH-08149; ETH-08776; ETH-09988; ETH-09677; ETH-09655; ETH-00629; Rectovaginal fistulas = 9: ETH-08550; ETH-08744; ETH-09089; ETH-09178; ETH-09742; ETH-09775; ETH-00711; ETH-08875; ETH-09775; for a total of 15 fistulas

[855] Ureteral injury and obstruction: ETH-00685; ETH-08563; ETH-08429; ETH-08578; ETH-10040; ETH-09677; ETH-09655; ETH-10019; ETH-08764; ETH-09041; ETH-09763
Urinary complaints, Issue Reports not reported to FDA: ETH-09433; ETH-09711; ETH-09442
Urinary complaints, Issue Reports reported to FDA: ETH-08177; ETH-00649; ETH-00657; ETH-00521; ETH-08816; ETH-8904; ETH-08937; ETH-09294; ETH-09307; ETH-09832; ETH-09599; ETH-09631; ETH-09647; ETH-09818; ETH-09926; ETH-10052; ETH-10101; ETH-09204; ETH-09526; ETH-09541; ETH-09285; ETH-09979; ETH-08398; ETH-08723; ETH-08914; ETH-09662; ETH-09733; ETH-09052
Defecatory dysfunction, Issue Reports not reported to FDA: ETH-09711; ETH-09018
Defecatory dysfunction, Issue Reports reported to FDA: ETH-08875; ETH-09541; ETH-09338; ETH-09285; ETH-09583
Allergic reaction, Issue Report reported to FDA: ETH-08519
Unknown/other, Issue Reports not reported to FDA: ETH-10108; ETH-10139; ETH-09864; ETH-09393; ETH-09233; ETH-00588
Unknown/other, Issue Reports reported to FDA: ETH-10061; ETH-09960; ETH-09837

[856] ETH-08081 (stroke); ETH-08856 (myocardial infarction [heart attack])

compared to the actual frequency of complications in clinical practice. Ethicon even included a statement on its complaint reports that the data may not be accurate due to underreporting.[857]

Complaint/Adverse Event Review, continued

II. MAUDE review

A search of the Manufacturer and User Facility Device Experience (MAUDE) Database maintained by the U.S. Food and Drug Administration produced the following for the period January 2005 through May 2010.

Two Hundred Thirty-Four (234) records of reported adverse events occurring between September 2005 and May 2010.

A. Two Hundred Thirty-Three (233) reported "injuries" (followed by listing of injuries)

B. One (1) reported "death" February 22, 2008

Analysis

1) Somehow, Ethicon's search of the MAUDE database did not reveal **the 2007 death of a woman due to uncontrolled bleeding at the time of the Prolift procedure**. There is no indication that Ethicon did anything to correct this underreporting.

2) Although the first paragraph stated that the MAUDE Database was searched from January 2005 through May 2010, the second paragraph referred only to September 2005 through May 2010. Ethicon gave no explanation for excluding events that occurred between January and September 2005.

3) Starting in March 2005 (when Prolift was launched) through August 2005, which represents the time period Ethicon excluded from its search of the MAUDE database, Ethicon received 18 complaints, only 2 of which were reported to the FDA. Complaints not reported to the FDA included 3 cases of bladder injury,[858] 2 cases of pain,[859] 1 hematoma,[860] and 10 product complaints. Four of these 10 product complaints involved Prolift components missing from the kits,[861] 3 cases in which the components fell or popped out of packaging before reaching the

[857] ETH-80635: Ethicon complaint reporting statement on Prolift, Bottom of form: "Data presented may not represent an accurate complication rate due to underreporting."
[858] ETH-08132, ETH-08108, ETH-08071
[859] ETH-08125, ETH-00730
[860] ETH-08055
[861] ETH-08114, ETH-08101, ETH-08092, ETH-08076

sterile field,[862] 2 cases in which the mesh tore,[863] and 1 case with a faulty handle of one of the kit components.[864]

Complaint/Adverse Event Review, continued

III. Internal versus MAUDE Database Complaint Review Experience

Internal complaint review records, as indicated above, by comparison to the MAUDE Database information compare in an as expected manner for the period January 2007 through May 2010. As indicated, the overall count of internal review complaints nearly doubles MAUDE reported events. The difference is associated with Ethicon reviewing every complaint whether representing potential clinically defined harm or otherwise, e.g. packaging complaints. In comparing clinically significant complaints, the two databases match in a consistent manner, e.g. MAUDE reported a total of 98 instances of mesh exposure/erosion (the single largest category of complaint) and the internal complaint review accounts for 91. Another example of relative comparability is the reported instance of infection. MAUDE indicated 17 and the internal review indicated a total of 25. These instances of comparable and variance (MAUDE to internal and internal to MAUDE) suggest good diligence in the internal review process which in some cases produces more exacting assessments due to the detailed investigative follow-ups taking place which don't always get reflected back in the MAUDE database. In summary, the differences encountered between the two data sets are not numerically significant and suggest that they each are highly representative of the complaint performance of the device across the patient/physician population.

Analysis

1) Ethicon misstated the dates of review, which were for different time periods regarding the MAUDE database, September 2005 through May 2010, versus the internal complaint review, January 2007 through May 2010. Therefore, the MAUDE database review covered a time period of 57 months, whereas the internal complaint review covered a time period of only 41 months. Then, Ethicon set out to compare the complaints across those time periods as if they were actually comparable.

2) Although Ethicon claimed that it reviewed each complaint for "potential clinically defined harm," this standard apparently did not apply as to whether complaints were reported to the FDA or not. As detailed above, Ethicon withheld many clinically significant complaints from the FDA. Again, this indicates that Ethicon was using its review process to report complaints only selectively, which minimized knowledge of complications due to the Prolift product and procedure, and portrayed the Prolift as safer than it actually was.

[862] ETH-08097, ETH-08061, ETH-08067
[863] ETH-08141, ETH-08120
[864] ETH-08136

3) Ethicon apparently regarded complaints related to performance of the Prolift kit itself in a different category and assumed that these complaints had no clinical significance. However, some of the kit complaints reported that the Prolift mesh implant tore during insertion, surely an event with clinical consequences for the patient if the Prolift mesh was not properly implanted. The Prolift surgical technique document states that "It is essential to install all of the available mesh straps to properly place and secure the implants."[865] Therefore, tearing of the Prolift mesh straps during insertion has clinical importance, yet Ethicon did not address this in any way and didn't even consider those complaints to have clinical significance. Moreover, Ethicon apparently did no testing of the Prolift mesh implants to determine why they were tearing during implantation and took no steps to correct this significant defect in the design and/or manufacturing processes of the Prolift mesh implant.

Furthermore, Ethicon did not address the complaints about missing kit components and faulty handles of the kit device. At the very least, Ethicon should recognize that these complaints indicate substantial failings within their quality control processes, that Prolift kits were commercially available without even containing all the necessary components for surgeons to perform the Prolift procedure. In fact, deficiencies in Ethicon's quality control processes ultimately led to a voluntary recall of the Prolift kits, in which Prolift kits labeled total only contained the anterior Prolift mesh implant (see below for further discussion).

Even more alarming, Ethicon received complaints of contaminated Prolift kits, where hair was found inside the newly opened kits.[866] Again, Ethicon failed to report these incidents to the FDA and apparently failed to address the marked deficiencies in its quality control processes that allowed such obvious shortcomings to occur and continue.

4) As noted above, the time periods of complaint review for the MAUDE database and the internal Ethicon complaint review were markedly different. Nevertheless, Ethicon claimed comparability of findings related to mesh exposure/erosion in the MAUDE database and internal complaint review. The MAUDE database recorded 98 incidents of erosion/exposure, while the Ethicon internal review process recorded 73 incidents of vaginal mesh exposure, 4 of gastrointestinal "exposure," and 14 of urinary tract erosion. Obviously, the clinical significance of gastrointestinal "exposure" and urinary tract erosion is vastly different than that of vaginal mesh exposure, yet Ethicon conflates and combines these incidents as if they belong in the same category of complications. Furthermore, Ethicon offered no explanation for the difference between the number of incidents in the MAUDE database versus the internal complaint review.

5) Again, despite the marked difference in the time periods covered, Ethicon went on to compare reporting of infection. Ethicon claimed "relative comparability" with 17 instances of infection in the MAUDE database and 25 instances of infection in the internal complaint review. Despite Ethicon's claim to relative comparability, the difference between 17 and 25 is a 32% difference in reporting. That is to say, Ethicon's internal complaint review underreported the

[865] ETH.MESH.00419572
[866] ETH-08270; ETH-08503; ETH-09258

frequency of infection by a factor of one-third, compared to the MAUDE database. Yet, Ethicon held this out as an example of "relative comparability" between the two datasets. Far from representing "good diligence in the internal review process," this represents a dramatic degree of underreporting of complaints received by Ethicon.

6) Ethicon concluded that the "differences encountered between the two data sets are not numerically significant." As discussed above, this conclusion is false and misleading, based on the information as presented. Ethicon also concluded that these databases "are highly representative of the complaint performance of the [Prolift] device." Nowhere does Ethicon address the well-known fact that each database represents a vast underreporting of the adverse events that occur in clinical practice.

IV. Product Recall

Based on the available information at the date of this report, there have been no recalls of this device.

Analysis

In April 2007, Ethicon voluntarily recalled lots of Prolift that were labeled as the total kit but contained only the anterior Prolift mesh implant.[867] As noted previously, given that no other Clinical Expert Report exists between January 2005 and the current report, this information about the Prolift recall should have been included and discussed. Clearly, that such a recall was necessary demonstrates a deficiency in quality control of manufacturing processes for the Prolift kits. That Ethicon claimed incorrectly that no recalls had occurred, failed to even mention the recall, much less address its root cause and solution, again demonstrates Ethicon's lack of integrity in the reporting process.

F. Risk/Benefit Analysis

In accordance with established Ethicon Inc Research & Development, Quality Engineering, Quality Assurance, and Medical Affairs departmental and company procedures/processes *(including the adoption of ISO 14971 [supporting procedural documents are available as required])*, an in-depth analysis of the Gynecare Prolift complaints and investigation outcomes has been conducted. The analysis produces an overall residual risk score and an assessment of overall residual risk level attributable to these devices.

The underlying factors of harm and hazard and their associated severity of harm and estimated frequency of harm together with complaints data and number of devices distributed are used to arrive at the overall risk score and the assessed overall residual risk level. Please see Table I and Table II below for a summary of these factors.

[867] ETH-17875

Table I: Harms/Hazards Summary Table, listing of 13 harms, severity of harm, hazard, and frequency of harm rating

- Unintended tissue reaction, frequency of harm rating = 4
- Blood loss, frequency of harm rating = 4
- Dermal/fascia tissue damage, frequency of harm rating = 4
- Internal organ injury, frequency of harm rating = 6
- Nerve damage/pain, frequency of harm rating = 8
- Neurological deficit, frequency of harm rating = 4
- Delayed wound healing, frequency of harm rating = 4
- Exposure – GI, frequency of harm rating = 4
- Exposure – Vaginal, frequency of harm rating = 8
- Exposure – UT, frequency of harm rating = 6
- Fistula formation, frequency of harm rating = 4
- Infection, frequency of harm rating = 8
- Failure of treatment, frequency of harm rating = 4

Table II: Harms Estimation Table

Frequency 0, extremely remote, ≤ 1/100,000 (or ≤ 10 dfm)
Frequency 2, remote, ≤ 1/50,000 (or ≤ 20 dfm)
Frequency 4, unlikely, ≤ 1/10,000 (or ≤ 100 dfm)
Frequency 6, low, ≤ 1/5,000 (or ≤ 200 dfm)
Frequency 8, rare, ≤ 1/1,000 (or ≤ 1000 dfm)
Frequency 10, more than rare, > 1/1000 (or > 1000 dfm)
Per number of devices or procedures as dictated by nature of device.
DFM: defects per one million devices or procedures as dictated by the device.

Analysis

1) This rating system for frequency of harm is not logical. Even with the shortcomings of the literature review section, described above, it seems pointless for Ethicon to gather these data about the frequency of complications due to the Prolift product and procedure, and then apparently ignore them in its assessment of the frequency of harm in its risk/benefit analysis. Moreover, the "hazards" that Ethicon claimed to be associated with the stated harms again reveals Ethicon's bias in attempting to portray complications due to the Prolift procedure as only occurring when something "improper" is performed, as opposed to complications occurring as a virtually inevitable outcome of the deficiencies and shortcomings of the Prolift product and procedure itself. One of the most obvious examples is the frequency of harm for vaginal mesh exposure.

Ethicon claimed that the "hazard" for vaginal mesh exposure was "local irritation/transitory foreign body response, improper implant positioning, and improper wound closing." First, the foreign body response to the Prolift mesh implant is emphatically NOT transitory; as detailed above, it is chronic. Moreover, the intensity of the foreign body response is directly related to the surface area of the mesh implant, and the Prolift mesh implants provide a very large surface area of foreign body.[868]

Second, Ethicon has never provided any evidence that vaginal mesh exposure is due to improper implant positioning. Although Ethicon has consistently claimed that full-thickness vaginal dissection for Prolift mesh implantation will decrease the frequency of vaginal mesh exposure, evidence in the medical literature contradicts this, with no significant difference in vaginal mesh exposure whether the mesh is implanted under the full thickness of the vagina, whether it is implanted under the vaginal layer as dissected for traditional anterior colporrhaphy, or whether it is implanted over plication stitches of traditional anterior colporrhaphy and then covered by the vaginal epithelium. Although some experienced Prolift users claim a very low frequency of vaginal mesh exposure, Ethicon itself does not believe these claims,[869] and other clinicians have indicated that even if such claims of very low frequency of vaginal mesh exposure are true, it cannot be assumed that most surgeons will be able to obtain similar results.[870]

Third, Ethicon has never provided any evidence that vaginal mesh exposure is due to improper wound closing. These unsuccessful attempts by Ethicon to blame surgeon technique for Prolift complications, rather than intrinsic deficiencies of the Prolift product and procedure itself, are typical of Ethicon's false and misleading statements that minimize the virtually unavoidable complications that occur as a result of permanent Prolift mesh implantation through the contaminated surgical environment of the vagina in transvaginal prolapse surgery.

As another point of evidence against Ethicon's claimed hazards, vaginal mesh exposure after Prolift mesh implantation can occur at any time, even years after the index Prolift

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[868] ETH-70371: from drawings, Total Prolift mesh implant = 60.7 in.^{2}; Anterior Prolift mesh implant = 42.3 in.^{2}; Posterior Prolift mesh implant = 24.7 in.^{2}

[869] ETH.MESH.00851319, email 1-21-2010, from Piet Hinoul: "Who believes Mr Lucente's group when Van Raalte publishes that they have NO erosions? Nobody!"

[870] Roundtable: Using mesh to repair prolapse: Averting, managing complications. Karram MM, moderator. OBG Management 2009; 21 (2): 21-28. Dr. Walters: "Some surgeons tell me that their own extrusion or erosion rate is lower than the published rate of 5% to 17%, but it is impossible to be certain of the long-term outcome in any patient unless she is followed carefully. The patient may consult another physician about her complications. The primary surgeon – even an expert – often does not know the actual mesh complication rate. That said, I am sure that some surgeons are particularly adept at using mesh kits for prolapse repair, thereby keeping their mesh complication rate low. The 5% to 17% number is what most gynecologic surgeons should expect for their patients."
Iglesia CB et al. Vaginal mesh for prolapse: a randomized controlled trial [reply]. Obstet Gynecol 2010; 116: 1457. ""Furthermore, if a group of trained surgeons cannot achieve the results of a few mesh experts, then it is unlikely that general ob-gyns around the world, who do mesh repairs in even lower volumes, will achieve excellent results. … "If expert surgeons from multiple institutions cannot get the outcomes of a few individuals, perhaps there is something wrong with the procedure."

procedure. This conclusively argues against Ethicon's claims that vaginal exposure is due to "local irritation/transitory foreign body response, improper implant positioning, and improper wound closing."

Finally, Ethicon assigned a frequency of harm to the category of vaginal mesh exposure of 8, meaning "rare, ≤ 1/1,000 (or ≤ 1000 dfm)." In the literature review section of the 2010 Prolift Clinical Expert Report, vaginal mesh exposure was reported at a frequency of 3.2% to 19.3%. How Ethicon can describe vaginal mesh exposure as "rare" is a mystery. Even if vaginal mesh exposure were calculated with the denominator of units of Prolift sold (an inappropriate technique, as discussed previously), using the frequency of vaginal mesh exposure documented by literature review, that calculation results in a frequency of 3 to 19 incidents per 1000 units sold.[871] Obviously, even that frequency exceeds the "rare" characterization of "≤ 1/1,000."

2) As noted above related to the Complaint Summary table, Ethicon failed to define or describe the categories of harms, and Ethicon failed to include a comprehensive list of all types of complications due to the Prolift procedure. If presumably the Risk/Benefit analysis should assess all risks related to the Prolift product and procedure, by failing to include all such risks, Ethicon underestimated the frequency of harm due to the Prolift product and procedure, and therefore, skewed the results of the risk/benefit analysis to inappropriately favor the unsupported conclusion that Prolift's performance was safe.

Material risks that Ethicon excluded (or, at the very least, failed to include) comprise mesh retraction; urinary issues (e.g., incontinence, dysuria, frequency, urgency, retention, voiding dysfunction); bowel issues (e.g., defecatory dysfunction including obstructed defecation, dyschezia [pain with bowel movements], urgency); known need for retreatment, most often reoperation, for mesh-related and other Prolift complications (most frequently, but not limited to, reoperation for mesh exposure and retraction), and the subsequent added morbidity of such reoperations; and the entirely new category of complications caused by blind passage of the Prolift trocars and permanent Prolift mesh implantation in non-vaginal, non-pelvic tissues that were previously healthy. By excluding these material risks and the well-documented need for treatment, Ethicon sought to minimize the true risks due to the Prolift product and procedure in such a way that a conclusion could be drawn that Prolift was safe. This conclusion was based on a fundamentally flawed process with incomplete and inaccurate data.

Risk/Benefit Analysis, continued

The analysis outcomes for Gynecare Prolift Pelvic Floor Repair System are as follows:
Overall Residual Risk Score = 68
Overall Residual Risk Level = High

Analysis

[871] 3.2% × 96,438 units per 1000 units = 3 per 1000 units; 19.3% × 96,438 units per 1000 units = 19 per 1000 units.

The overall residual risk score for Prolift of 68 apparently corresponds to a simple addition of the frequency of harms rating, listed above. As discussed previously, this number has no meaning and no basis in fact. The frequency of harms rating drastically underreports the true frequency of complications due to the Prolift product and procedure. Moreover, the list of 13 hazards that Ethicon identified is in no way a comprehensive list of complications due to the Prolift product and procedure; and minimizes Prolift-caused complications, to conclude that Prolift's "safety" is such that it can continue to be marketed. If Ethicon truly acted in accord with the Johnson & Johnson credo and held patient safety as its highest priority, Ethicon would not devise and implement a risk/benefit analysis system that so glaringly misrepresents the true range and frequency of complications due to Prolift. It seems more than likely that IF Ethicon did truthfully represent the full range and markedly high frequency of complications due to Prolift, the only unbiased and patient-responsible conclusion would have to be that Prolift is NOT safe enough to continue to be marketed and that the magnitude and severity of the risks far outweigh the benefit, if indeed there is a benefit at all to the Prolift.

Risk/Benefit Analysis, continued

According to the procedures and practices consistent with regulatory guidelines and company policy, the above scores and assessments indicate the need for a complete Risk/Benefit analysis. As a result of this process and a thorough review of all other pertinent information, including: a detailed clinical literature review as provided in Section C of this report and the complaint reviews (internal and MAUDE Database) as provided in Section E, the overall residual risk associated with Gynecare Prolift is considered acceptable in view of well documented benefits/patient outcomes.

Analysis

1) Although Ethicon claimed to have performed a detailed clinical literature review, only 50 references were cited, and of these, 9 referred to compiled abstracts from the International Urogynecologic Society [sic], 2 were duplicates, and 3 did not include complete citation information although that was available at the time this report was completed in July 2010. Given that other literature reviews have included hundreds of references, Ethicon's list of references cannot possibly be considered complete. This in no way represents "a compilation of relevant scientific literature that is currently available" as stated in the very beginning of this report.

2) In addition, the literature review is incomplete in another way, in that material categories of complications were excluded, as discussed above. Moreover, Ethicon never provided a quantitative summary statement of risk that combined the frequencies of different complications, in order to provide an overall risk assessment of the Prolift product and procedure based on the literature review.

3) Ethicon claimed to provide a review of internal complaints and the MAUDE database in order to inform its risk/benefit analysis. However, as detailed above, that review could not possibly have represented a comprehensive review of all Prolift-related complaints that Ethicon was aware of. The review of both the internal complaints and the MAUDE database did not fully cover the time span since Prolift launch. Ethicon listed only 13 categories of complaints, did not define those categories, and did not provide a comprehensive list of complaints received. Ethicon underreported the number of complaints in the Complaint Summary table compared with Issue Reports received with Prolift-related complaints. Moreover, Ethicon failed to include the known additional morbidity incurred by treatment of Prolift-caused complications.

4) Finally, Ethicon concluded that "the overall residual risk associated with Gynecare Prolift is considered acceptable in view of well documented benefits/patient outcomes." Ethicon provided no evidence or process as to how it arrived at the judgment of "acceptable" risk of Prolift. Ethicon provided no quantitative summary estimate of the "benefit" accorded to Prolift. Based on the literature review in this Clinical Expert Report, the claim that Prolift provided "well documented benefits/patient outcomes" is false and misleading. At most, based on weak evidence, Prolift may provide a small incremental benefit in anatomic outcomes restricted to anterior vaginal prolapse repair. No evidence supports the claim that Prolift provides any benefit as to patient-oriented outcomes, and indeed the available evidence has demonstrated conclusively that Prolift did NOT provide any benefit as to patient-oriented outcomes. Considering that the crux of this entire report rests on the conclusion drawn from the risk/benefit analysis, the fact that Ethicon had such weak evidence of the benefit of Prolift is telling in the extreme. Any unbiased observer would have to conclude that the risks of Prolift vastly outweigh the benefits and that the Prolift product is not sufficiently safe to be marketed.

XVII. The Prolift + M Was Developed and Marketed as an Improvement Over the Prolift

An alternative to the Prolift was a product developed by Ethicon, the Prolift + M. The Prolift + M is virtually identical to the Prolift in terms of instructions, indications, and surgical technique, with minor shape modifications, but includes the partially absorbable Ultrapro mesh rather than Gynemesh PS mesh. The Prolift +M would be lighter and leave less mesh in the woman's body after the monocryl would absorb, which would be safer than the full mesh load implanted with the Prolift.

Even before the Prolift was first marketed, people within Ethicon were discussing the use of Ultrapro rather than Gynemesh PS mesh for this system, based upon Ethicon's expectation that the partially absorbable Ultrapro would leave a mesh implant with larger pores, less material, less density, and more elasticity, and thus result in better safety and efficacy.

For example, on January 14, 2005, Engineering Fellow Gene Kammerer sent the following email to Dr. Dieter Engel and to Zenobia Walji:

Dieter,

Sorry we didn't get a chance to talk last week when you were in Somerville. I wanted to discuss with you the possibility of using the UltraPro mesh for pelvic floor repair in place of the Gynemesh. I think this could be the next advancement for pelvic floor repair. Without going into too much detail here, I will just say that this mesh could reduce the scar contraction and lower the density of the scar formation resulting in fewer cases of re-occurrence of the prolapse and erosion. If your interested let's set a time were we could talk for about an hour to get started.

(ETH.Mesh.0058229). Days later, in a January 18, 2005 email,[872] Gene Kammerer advised multiple individuals within Ethicon including Senior Scientist Kelly Brown, Ph.D. about a long list of criticisms of Gynemesh PS by Professor Mauro Cervigni, a respected surgeon experienced in the use of Gynemesh PS mesh in a tension-free fashion. Kelly Brown responded to this email and acknowledged the "commonalities in surgeons' observations."

Thereafter, in a May 13, 2005 memorandum, Gene Kammerer analyzed: "Use of Ultrapro Mesh for Pelvic Organ Prolapse (POP) Repair through a Vaginal Approach." **The problems with the use of Gynemesh PS were described: "Mesh retraction ("shrinkage") is a more uncommon complication but it is considered more serious. It can cause a vaginal anatomic distortion, which may eventually have a negative impact on sexual life. Its treatment is difficult." The memorandum states: "In summary our conclusions are that placing the Ultrapro within the pelvic floor as a direct substitution for the Gynemesh PS is very reasonable. The benefits of using the Ultrapro were thought to include: significantly reduced amount of material, lower inflammatory response, more stable scar matrix, potentially less scar formation and reduction of the complications of mesh exposure and erosion, vaginal pain and distortion.**

In an email exchange in January, 2006 and February, 2006[873] several Ethicon scientists and others discussed the TVM group's dissatisfaction with Gynemesh PS as a mesh material, since in the words of Bob Roda on January 24, 2006: "the Prolene Soft material over time contracts. Thus creating the potential for failures and low erosions. What they would like to see is what materials that we might be able to create that would provide the scaffolding for the repair without the limitations they feel Prolene Soft has." Bob Roda then states that he wants to set up a meeting in Hamburg for key opinion leaders "to look at some potential prototypes of various mesh configurations," and indicates: The Tissue reinforcement team have just completed an initial meeting looking at next generation mesh materials, etc…." This is then addressed by Gene Kammerer, who first refers to a "next gen mesh" project that he wanted to resurrect on February 13, 2006 (presumably Thunder – see below). He then states:

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872 ETH-18761-18763.

873 ETH.MESH.00585937-00585939.

> A shorter term solution, as defined by the Mesh team last year, was to substitute the UltraPro directly for the PS. Some European surgeons are already doing this and Axel had identified a couple. A moderate term solution was to change the knit construction of the UP to be more like the PS or alternatively substitute some Monocryl fiber into the PS. The benefits here are less material left behind, eventually; a low foreign body response with Monocryl vs Vicryl; no ngative baggage associated with the Monocryl in pelvic floor; as with Vicryl; and a short, relatively, discovery and development time, as well as a more straight forward regulatory path, which we have already investigated.
>
> **I met with both Dr. Cosson and Prof. Jacquetin at the Parris meeting in 2004. They expressed an interest in a new mesh to control and reduce scar contraction. This lead us, Axel and I to investigate, the UP vs PS conversion. The results of the investigation showed us that it could be done and we could possible get an enhanced product. The team wanted to move forward, but then everyone got re-assigned, and so the project kind of went into limbo.**

These emails demonstrate that the French TVM group had determined at least as of 2004 (with Ethicon's knowledge) that Gynemesh PS caused too many complications (i.e. scar contraction) related to the mesh material to be safe. This was expressed to Gene Kammerer at that time. Despite this knowledge, Ethicon inexplicably let the issue drop ("the project kind of went into limbo"), and went ahead and marketed the Prolift with Gynemesh PS mesh.

In a July 19, 2006 PowerPoint addressed Project LIGHTning, by Peter Meier,[874] the following statements made:

> In vitro testing results of Ultrapro (UP) show:
> - UP acts like biological tissue, better than Gynemesh PS
> - UP is softer than Gynemesh PS…
> - UP is lighter than GPS…
> - Strength of UP is comparable to GPS…
> - Ultrapro has larger pore size than GPS (3-5mm compared to 0.3-2.4mm)

Thereafter in the December 12, 2006 LIGHTning Project Charter[875] there are numerous statements, Unmet Needs, and value propositions confirming Ethicon's belief that Prolift M was a better, safer medical device than the Prolift. For example:

> Project Scope: Fast upgrade of PROLIFT System to a new mesh to retain market share.

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874 ETH.MESH.00892391.

875 ETH.MESH.00267733-00267872.

…

Key Customer Needs
1. Less complications (increase quality of life)
2. Less foreign material (lightweight concept)
3. Soft and easy to use

Customer Needs
- Non-negative inflammatory reaction* as compared to GPS!
  (to solve the Unmet Need of: Minimize shrinkage, vaginal stiffness, dyspareunia, and permanent pain (Improve Quality of Life!)

Ethicon has produced numerous documents indicating that Ethicon believed the Prolift +M to have safety advantages over the Prolift. For example, in the context of preventing pores from losing their size when implanted, and preventing "shrinking and curling of the mesh," Piet Hinoul states in a September 3, 2009 email, "…the more rigid +M mesh offers better stress shielding." (ETH.MESH.00816396-00816398). The Prolift +M clinical strategy is quite telling:

> **Mesh exposure is a common complication which can be managed by excision and closure. Mesh retraction ("shrinkage") is less common but it is considered more serious. It can cause vaginal anatomic distortion, which may eventually have a negative impact on sexual function. Its treatment is difficult. Additionally, the scar plate that forms with in-growth of tissue into the mesh can cause stiffness of the vagina that further impacts sexual function in a negative manner. In an effort to minimize these complications, the use of a lighter-weight alternative mesh for POP repair is being explored. This mesh would serve to replace the Gynecare Gynemesh PS used within the Gynecare Prolift Pelvic Floor Repair system.**

The Prolift +M Expert Report authored by David Robinson, dated February 5, 2008, first summarizes medical literature with regard to the Prolift, and notes that, "No clinical investigations have been conducted on the use of Gynecare Prolift Pelvic Floor Repair System." In the next section the rationale for the change in materials is discussed:

> **However, implantation of polypropylene mesh is associated with an increase in problems associated with the foreign implant material. Complications associated with these materials have led to changes in implant materials and construction with a goal to 1) reduce implant mass and 2) increase the mesh pore size.**
>
> **…**

> **Reduction of the mass and the increase in the pore size of the mesh implant foreign body are seen to alter the inflammatory response which in turn is likely to alter tissue ingrowth and the resulting properties of the reinforced tissue. As the mass of a mesh implant is reduced and the pore size in increased, the surface area exposed to the host is reduced, and the foreign body reaction to the implant is reduced.**

(ETH.MESH.00000072-00000086).

The presentation by Howard Goldman, M.D. titled "Material Science Considerations" provides an analysis of reported Prolift complications and then details the expected improvements due to the change in mesh material in the Prolift +M, including improved biocompatibility due to reduced foreign body/surface area, large pore size, stress resistance, elasticity/flexibility, and a minimized foreign body response. "Large pores that minimize scar plate formation 'bridging fibrosis'." (ETH.MESH.00001401-00001419).

Ultimately, the use of Ultrapro was developed and utilized as the material of the Prolift + M, which was launched in about February 2009. As described, Ethicon has produced multiple documents attesting to its belief that the Prolift + M offered improved surgeon handling, safety, and efficacy as compared to the Prolift.[876] The Prolift +M marketing and sales documents demonstrate that the Prolift +M was marketed as an improvement over the Prolift. For example, in a sales aid titled: "biocompatibility is the science of living better," numerous statements as to the superiority of the Prolift +M as compared to the Prolift.[877]

Statements by Vincent Lucente, M.D. in an Ethicon webinar held in December, 2008 reflect Ethicon's beliefs regarding the advantages of the Prolift +M as compared to the Prolift.[878] Scott Jones confirmed that the Project Lightening commercialization strategy provided for the cannibalization of the Prolift within 1-2 years.[879] A PowerPoint dated June 18, 2007 and September 20, 2007, with Clifford Volpe and Peter Meier's names on the cover, indicates "The Benchmark is Ultrapro." This is yet another documentation of Ethicon's belief in the superiority of Ultrapro over Gynemesh PS, since Prolift +M was still a year and a half away from launch. This statement, the statements in the Gene Kammerer emails, and the documentation as to the

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876 ETH-60406: June 18, 2008
"PROLIFT +M will be positioned as the extension to the PROLIFT family but with improved patient experience in mind. PROLIFT +M will target customers who are interested to answer the question whether les graft material will improve functional outcomes and patient quality of life.
Our value propositions are clear:
- To the patient: PROLIFT +M offers less foreign material in the pelvis that may lead to a softer and more dynamic repair
- To the Surgeon: PROLIFT +M offers the same delivery system and feel out of packet as PROLIFT, with the opportunity to improve subjective outcomes"
ETH-60760: 10-29-2008, email from Jonathan Meek

877 ETH.MESH.00908372-00908377.

878 ETH.MESH.000067354.

879 Scott Jones dep., 743:21-744:18; 745:17-746:18; 749:16-750:16.

basis for marketing the Prolift +M, belies the statement in Axel Arnaud's 2005 "Graft or No Graft" presentation: "no scientific evidence suggesting to use something else than polypropylene."

XVIII. Project Thunder

> Ethicon clearly recognized the high frequency and severity of mesh complications with the Prolift Systems due to the use of polypropylene mesh, which Jonathan Meek referred to as "the best of a bad lot…"[880] As a result, Ethicon determined that it was necessary to develop an understanding as to the dynamics of the pelvic floor (years after telling physicians and patients that Ethicon had developed a "revolutionary" treatment for the pelvic floor), and ultimately a new mesh material, and initiated Project Thunder, described by project leader Clifford Volpe.[881]

In a May 9, 2008 Power Point titled "Thunder MGPP decision meeting," significant statements are made demonstrating that Ethicon knew about the inadequacies of the Prolift, and serious problems with safety and efficacy.

1. There is still NO evidence of a Device created specifically for the female pelvis.

2. Thunder will be the first Device specifically developed for Female Pelvic Floor.

3. There is a need for a Unique and Proprietary Material (It cannot be what we currently known as mesh).

4. There is no patient-centric PF material!

5. Pelvic Floor materials are still over-engineered.

6. We need less foreign body material.

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[880] ETH-60667: 10-29-2008, email from Jonathan Meek
"Key Point: PP [polypropylene] is the best of a bad lot re integration, retraction and there is a need to develop grafts that mimic the human tissue mechanical properties."
ETH-47699: 11-12-2008, email from Scott Jones
"Polypropylene creates an intense inflammatory response that results in rapid and dense incorporation into the surrounding tissues. …"

[881] Clifford Volpe dep., 152:19-153:14; 154:13-155:3.

7. Need for materials that correlate to measured female pelvic physiological characteristics.

8. Stress shielding needed to avoid pore-collapse, deformation and pre-stretch (with images of mesh under small loads, demonstrating reduced pore size due to collapsed pores).

9. Different mechanical properties are needed in different area of PF.

10. Benefits of Thunder compared to current PFR Products included:
    - Minimal folding, erosion
    - Less permanent deformation, shrinkage, pain
    - Elasticity adapted to pelvic floor
    - Easier, less invasive procedure
    - Improved foreign body mass
    - Long term effectiveness

11. The Requirements for Thunder included, in the context of shrinkage/stiffening:
    1. pore size>3 mm
    2. pore size>1 mm under stretch

In the August 25, 2008 T-Pro Pipeline Leadership Team, Stage Gate: Discovery Initiation PowerPoint, Customer Needs are listed:

1. Ingrown graft to re-produce normal pelvic floor dynamics

2. Reduce vaginal stiffness, mesh exposure, pain

3. reduce the rate of tissue contraction and folding

4. Lower amount of foreign body mass

5. Easy to learn and use

6. Low recurrence rate.

The Design Elements include:

1. Stress shielding

2. Large Pore to implant ratio

Later in the presentation (p.13) illustrations demonstrate the reduction in effective porosity that occurs when force is applied to conventional polypropylene mesh. Finally, the T-Pro Requirements start with: "The less foreign material the better, Ultra-Lightweight concept with a high pore to implant area ratio."

Despite this extensive list of deficiencies Ethicon continued to market the Prolift, knowing that women would suffer severe and often intractable injuries and damage, and that when objectively viewed the risk benefit profile was unacceptable.

Lack of Consistent Post-Market Surveillance

I have reviewed the deposition and exhibits of Lynn Meyer of August 20, 2014.

Lynn Meyer was the designated deponent identified by Ethicon to respond to questions on the internal evaluation of and reporting of complaints to FDA related to Ethicon devices, including the Prolift System. Meyer is currently employed by Ethicon as a manager of post market surveillance; previously, she held positions in Worldwide Customer Quality (WCQ), which is the department within Ethicon responsible for identifying, evaluating, and reporting complaints related to Ethicon devices.

Ms. Meyer admitted to systematic inadequacies in the capturing, evaluating, and reporting of complications related to Ethicon devices. It is well known that complications are underreported in any system in which reporting is voluntary. The inadequacies in Ethicon's internal processes of complaint recording and reporting magnify this effect of underreporting, likely contributing to Ethicon's underestimated statements of the frequency and severity of complications related to Ethicon devices.

Complications known to Ethicon are not consistently reported to WCQ. Exhibits presented in
Meyer's deposition revealed several examples of complications known to Ethicon employees, including by a product director and medical affairs director, that were not reported to WCQ.
Although Meyer testified that Ethicon's procedures require that any Ethicon employee report a complaint to WCQ as soon as it becomes known, these procedures are not consistently followed, resulting in underreporting of these known complications. Apparently, there are no repercussions for failing to report such complications; in preparation for her deposition, Meyer did not ask the relevant Ethicon employees why these complications had not been reported.

In addition, there appears to be no procedure in place that requires the active monitoring of sources of complications related to Ethicon devices, such as reports in the medical literature and presentations at scientific meetings (which Ethicon employees regularly attend). Although Meyer testified that "our complaint procedure requires that literature articles be entered into our complaint database," she did not identify any procedure that required regular searches of the medical literature to capture complications related to Ethicon devices.

Further, there appears to be no procedure in place by which complications that occur to patients in Ethicon-sponsored studies are uniformly captured. For example, Ethicon funded Dr. Vincent Lucente to perform a study of the Prolift Systems; despite the fact that 85% of patients experienced at least one complication after Prolift surgery, Ethicon never even obtained the study data and thereby failed to capture, evaluate, and report this high rate of Prolift complications in WCQ and to the FDA.

Obviously, when complaints are not adequately captured, they cannot be evaluated internally, resulting in a falsely low representation of the complications related to Ethicon devices. Even when complaints are recorded in WCQ, Ethicon fails to report a substantial proportion of them to FDA. (In a review of 280 Issue Reports that I previously performed, 36% had not been reported to FDA.) Even in the complaints that are reported, Ethicon minimizes or denies the extent of patient injury and fails to draw the correct medical conclusion regarding the relation between the injury and the device. In one of the more blatant examples, despite testimony from several Ethicon employees that mesh erosion is related to Ethicon mesh products, in Issue Reports of mesh erosion, it is recorded that "no conclusion can be drawn at this time" regarding the relation between mesh erosion and the mesh device.

XIX. CONCLUSION

In the beginning, with Ethicon's backing, a group of French surgeons sought to develop a new way to help women with a bothersome problem, vaginal prolapse. Over the course of the next 10 years, Ethicon turned that effort into a medically unsafe, dangerous commercial product and procedure, the Prolift, that has devastated the lives of an untold number of women. The clinical and preclinical studies, medical literature, and internal documents regarding medical issues, establish an unsafe and unacceptable risk benefit profile.

One can be sure that the women known to be injured today represent only the proverbial "tip of the iceberg" when considering the number of women who have been or will find themselves harmed by the Prolift product and procedure. This is most unfortunate in light of the fact that numerous safer alternatives with comparable or superior efficacy (listed above) existed for the treatment of pelvic organ prolapse, a quality of life condition. It is my opinion that the Prolift was medically unsafe and should not have been available. To the extent the Prolift was to be marketed, this should have been limited to women with no other options, advanced prolapse that had failed all other options, and only with a thorough informed consent explaining the catastrophic risks.

The true scope of the damage done by the Prolift will only become fully evident with the passage of time, as tens of thousands of women who have had the Prolift implanted in their bodies move through their lives, age, and develop the well known complications such as contraction and erosion, and develop other medical conditions that will unmask latent complications due to the medically unsafe Prolift procedure and permanent Prolift mesh implantation, with its unacceptable risk benefit profile.

The path of the Prolift product and procedure can be traced over time. In development and design of the Prolift product, including the permanent mesh implant and the inserter tools designed to perform the Prolift procedure and only the Prolift procedure, Ethicon had internal processes, such as the DDSA and FMEAs, and clinical expert report, that were meant to prevent an unsafe product from reaching the marketplace. The processes failed to include all material risks of the Prolift product and procedure that Ethicon could reasonably foresee or to fairly and accurately evaluate the medical literature and internally available data and information; in addition, Ethicon assigned probabilities to the few risks that were included (termed hazards and harms) that had no medically reasonable basis. In this way, Ethicon moved the Prolift forward to commercialization, instead of correctly concluding that the substantial risks of the Prolift product and procedure could not be adequately mitigated. In brief, the Prolift was a poorly conceived, poorly designed product that should have never moved beyond the drawing board, and Ethicon should have abandoned it at that point.

Ethicon sponsored the "TVM" studies of the transvaginal mesh procedure invented by the French surgeons and subsequently procured by Ethicon for commercialization as the Prolift product and procedure. As a proxy for the Prolift, the immediate and 1-year results of the TVM studies provided Ethicon with sufficient evidence to determine that the procedure did not provide enough benefit to balance the tremendous risks incurred by the procedure, with blind trocar passes through not only deep pelvic tissue but also previously uninvolved areas of the hip, thigh, and groin, in addition to the result of permanent mesh implantation that initiated a chronic, severe inflammatory and foreign body reaction, with all the resultant clinical complications of mesh contraction and erosion, chronic pain, dyspareunia, and the inability of women to engage in normal sexual relations. The TVM studies demonstrated the inordinately high risks of the procedure, in particular, the extremely high rate of reoperation required to manage complications due to the TVM procedure, including mesh-related complications and recurrent prolapse due to failure of the procedure. At this point, if Ethicon examined these results objectively and with patient safety foremost in mind, Ethicon would have abandoned marketing of the Prolift product and procedure. The same holds true for the data compiled in the Gynemesh PS study, especially seen in the context of the data, literature, emails, and statements of the French doctors who were working to use Gynemesh PS to develop the TVM and Prolift procedures.

Despite its claims to benefit for the Prolift, Ethicon never performed any clinical studies of the Prolift that would have adequately demonstrated the balance between risk and benefit. Despite Ethicon's claims as to positive outcomes of the Prolift procedure, Ethicon never had any compelling clinical evidence on which to base these claims. The data that was obtained demonstrated an unacceptable risk benefit profile due to lack of true efficacy benefit, and numerous medically unreasonable risks, which were unnecessarily injected into the treatment of pelvic organ prolapse.

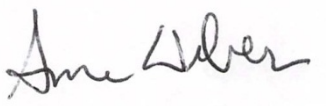
Ethicon had opportunities to revisit its own data in the TVM studies and the data in the medical literature, and make a decision as to whether the risks outweighed the benefits for the Prolift, as time went on and reports of complications flowed into the company. Unfortunately,

Ethicon failed to heed the accumulating data that Prolift harmed women in no way proportionate to its "benefit," which was supported by the weakest evidence at best. Ethicon ignored evidence that Prolift provided inadequate benefit in terms of outcomes important to women, such as relief of symptoms and avoidance of complications. Instead, Ethicon emphasized those few articles that demonstrated a "benefit" in terms of anatomic outcomes of prolapse repair, despite the fact that those same articles demonstrated no difference in symptom resolution or quality of life improvement. At this point, if Ethicon had objectively viewed the information, it would have concluded that the benefits of Prolift certainly did not outweigh the risks, particularly because the benefits were weak in the extreme and women remained at lifelong risk of Prolift mesh-related complications. At this point, if Ethicon had evaluated all the available data in an objective way, it would have concluded that the risks of Prolift greatly outweighed the benefit, if in fact a benefit existed at all.

Ethicon decided, albeit too late, to discontinue marketing the Prolift product and procedure as of September, 2012. Ethicon ultimately did so when faced with the choice of conducting rigorous safety studies as required by the 2012 522 Orders or withdrawing the Prolift from the market. (This is set forth in detail in the deposition of Brian Kanerviko and the exhibits cited therein).

Nevertheless, this still leaves tens of thousands of women in whom the Prolift product has already been implanted, and these tens of thousands of women remain at risk for, and many will suffer, the complications due to the Prolift procedure and permanent Prolift mesh implantation, as detailed throughout this report.

Very truly yours,



Anne M. Weber, M.D., M.S.

February 1, 2016